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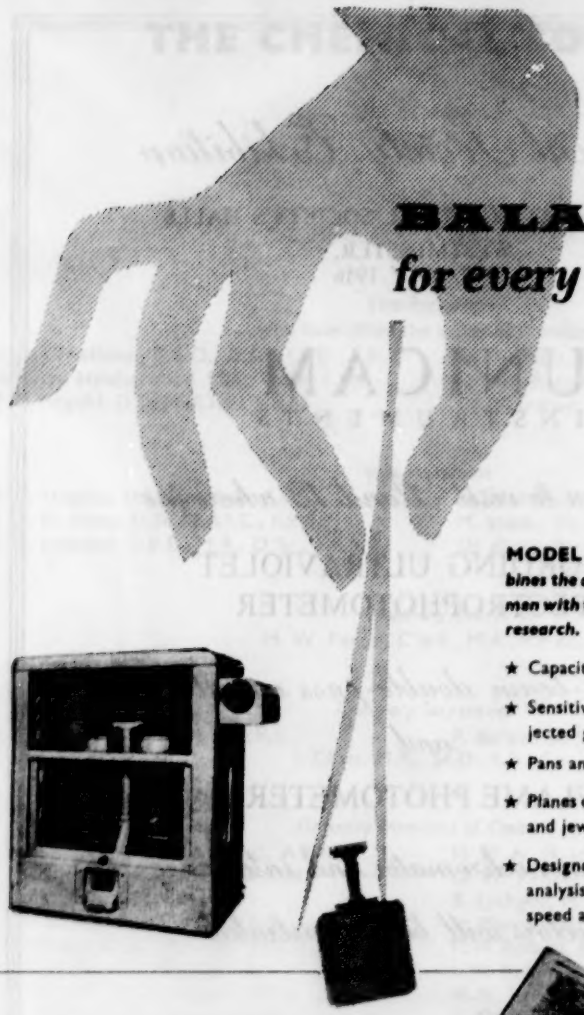

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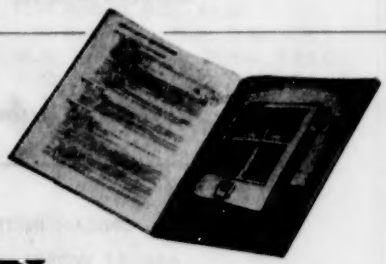

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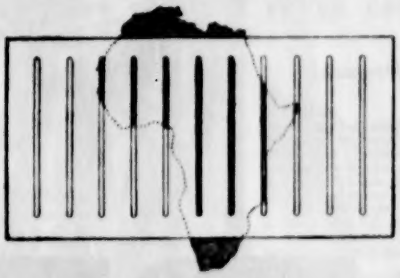

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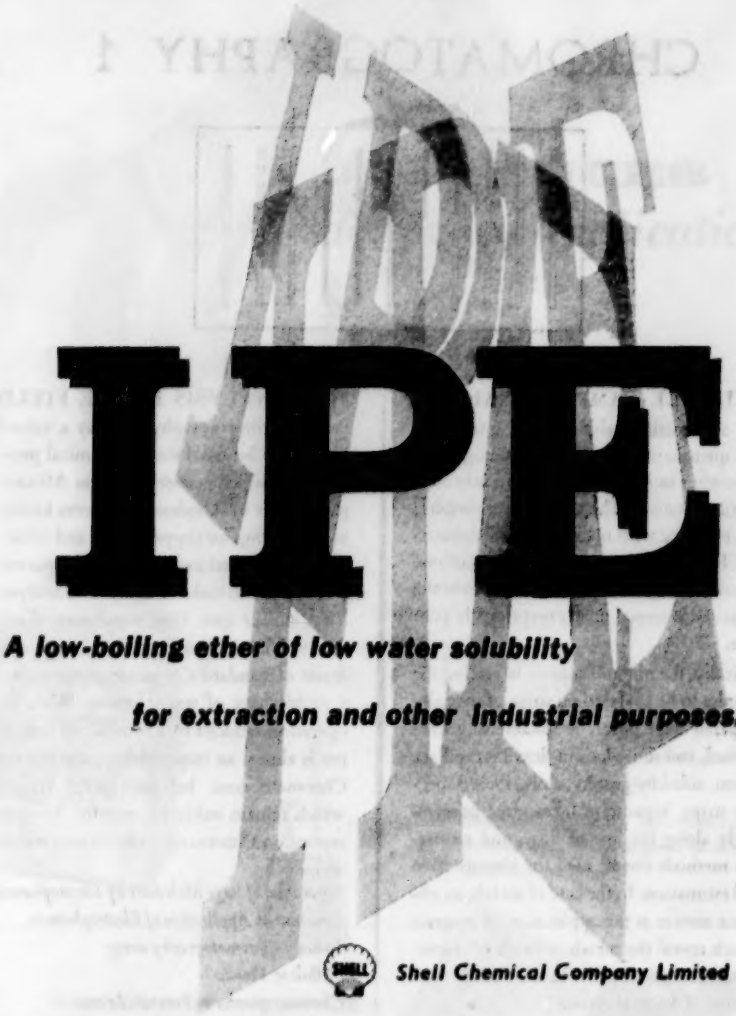

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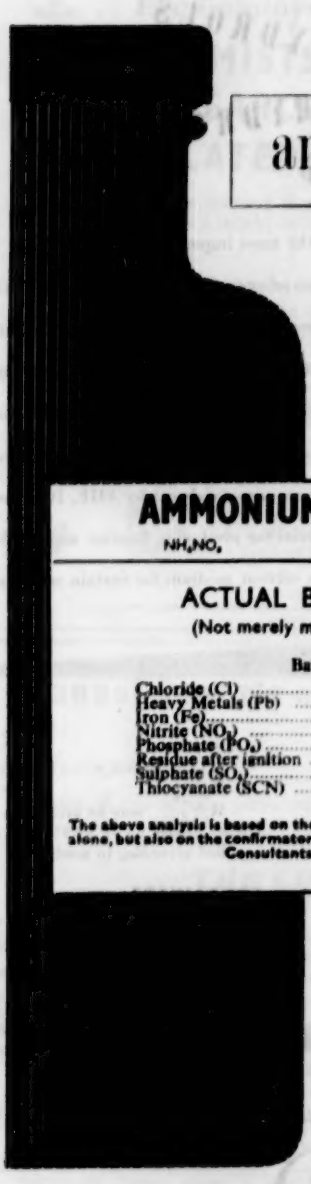

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171. *The Epimeric* (±)-1 : 3-*Diaminocyclohexanes.*

By F. R. Hewgill and P. R. Jefferies.

cis- and *trans*-1 : 3-Diamino*cyclo*hexane have been prepared by Schmidt reactions on the corresponding dicarboxylic acids. Contrary to the claim of Skita and Rössler [1] no inversion of configuration occurs in the Curtius reaction of the *trans*-dicarboxylic acid. Evidence in support of the configurations is given.

Merling [2] prepared a 1 : 3-diamino*cyclo*hexane, b. p. 193°/752 mm., d^{15} 0·956 (diacetyl derivative, m. p. 256°), by sodium–alcohol reduction of dihydroresorcinol dioxime, and a similar product is described by Kötz and Grethe.[3] The methods of preparation used by these and other authors are known to give epimeric mixtures, and in an attempt to distinguish the geometrical isomers Skita and Rössler [1] applied the Curtius reaction to the epimeric methyl hexahydro*iso*phthalates. Two dihydrazides were obtained but unexpectedly [4] each apparently yielded the same diethylurethane and diamine, b. p. 198° (picrate, m. p. 265°); the authors suggested that a Walden inversion had occurred during the conversion of one isomeric diazide (neither was isolated) into the diurethane. This diamine was identified with that of Merling,[2] and an attempt to prepare the other epimer by hydrogenation of *m*-nitroaniline afforded a picrate, m. p. 254°, from which a diamine, b. p. 202°, tentatively assigned the *trans*-configuration, was obtained.

No inversion was detected in the preparation of the epimeric 3-amino*cyclo*hexanecarboxylic acid by the Schmidt reaction,[5] and we now report the production of two discrete diamines in approx. 45% yield, isolated by an improved technique, when an excess of hydrazoic acid is allowed to remain in prolonged contact with the hexahydro*iso*phthalic acids. The characteristics of the epimeric 1 : 3-diamino*cyclo*hexanes so obtained from the corresponding hexahydro*iso*phthalic acids are given in the Table.

	cis	*trans*
B. p.	197—198°/760 mm. 46—48°/0·1 mm.	197—198°/760 mm. 46—48°/0·1 mm.
d_4^{20}	0·9515	0·9662
n_D^{20}	1·4911	1·4957
Diacetyl derivative, m. p.	263°	220—221°
Di-*p*-nitrobenzoyl derivative, m. p.	329—330°	240—241°
Dipicrate, m. p. (corr.)	275°	269°
Dihydrochloride, m. p.	>360°	330°

In view of these results it appeared highly improbable that inversion should have occurred under the milder conditions of the Curtius reaction. We therefore repeated the Curtius reaction, following as closely as possible the conditions specified by Skita and Rössler.[1] The dihydrazides closely resembled the two different entities described by these authors. The diazides were converted directly into their respective diethyl- and dibenzylurethanes. The diethylurethanes both had m. p. 146—147°, but on admixture this was depressed by some 30°, thus proving that although very similar they are different compounds. Moreover, the dibenzylurethanes proved to be quite different. To avoid possible inversion during hydrolysis of the diethylurethanes, the diamines were prepared by hydrogenolysis of the dibenzylurethanes, easily and in good yield by the use of W7 Raney nickel catalyst, and were identified as the epimers expected if no inversion had taken place. On hydrolysis of the *trans*-diethylurethane as described by Skita and Rössler, only the *trans*-diamine was obtained.

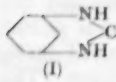
We therefore conclude that the Curtius reaction proceeds with the same stereochemical specificity as the Schmidt reaction in this case. The identity of the b. p.s of the diamines and of the m. p.s of the diethylurethanes is misleading. Moreover, the picrates could

[1] Skita and Rössler, *Ber.*, 1939, **72**, 461.
[2] Merling, *Annalen*, 1894, **278**, 36.
[3] *J. prakt. Chem.*, 1909, **80**, 503.
[4] Cf. Wallis and Lane, "Organic Reactions," Wiley, 1946, Vol. III, p. 272.
[5] Hewgill and Jefferies, *J.*, 1955, 2767.

be satisfactorily crystallised only from water: the use of aqueous ethanol failed to reveal the differences in crystalline form and gave a *cis*-picrate with practically the same m. p. as the *trans*-epimer.

To obtain some idea of the relative stability of the epimeric diamines and, if possible, to render them more accessible other methods of preparation were examined. The platinum-catalysed reduction of dihydroresorcinol dioxime, though very slow, gave a good yield of an epimeric mixture of diamines. Both the picrates and the acetyl derivatives of this mixture were easily separated into the pure epimers by fractional crystallisation, giving a *cis* : *trans* ratio of 6 : 1 and 8 : 1 respectively. Although Skita and Berendt,[6] and Skita and Rössler,[1] prepared the diamine by platinum-catalysed reduction of *m*-nitroaniline, this was found by us to yield mainly polymers, which were not identified. However, platinum-catalysed hydrogenation of *NN'*-diacetyl-*m*-phenylenediamine afforded a mixture of the epimeric hexahydro-compounds in fair yield.

Further evidence for the configurations assigned involved attempts to prepare the cyclic urea, 2 : 4-diaza*bicyclo*[3 : 3 : 1]nonan-3-one (I) which was finally isolated in small yield from the prolonged reaction between the *cis*-diamine and diethyl carbonate at a high temperature and pressure. Under the same conditions the *trans*-diamine afforded only polymeric material. It is apparent that ring closure of *cis*-1 : 3-disubstituted *cyclo*hexanes proceeds readily only at elevated temperatures, a condition conducive to the formation of the energetically less favourable diaxial conformation. This conjecture receives additional support from the failure of the *cis*-diamine to condense with carbonyl chloride under standard conditions. Reaction with ethyl chloroformate afforded the diethylurethane. It is known that phthalic anhydride reacts with hydrazoic acid to give some benziminazolone,[7] but hexahydro*iso*phthalic anhydride with hydrazoic acid gave only a mixture of the *cis*-diamine and amino-acid.



(I)

It will be seen from the Table that the values of the physical constants (except the b. p.) of the *trans*-diamine are higher than those of the *cis*-epimer. In addition, all the derivatives of the *cis*-diamine, except the diethylurethane, have higher m. p.s and lower solubilities than their corresponding *trans*-epimers. These results are in accord with the reversal of the Auwers–Skita rule for 1 : 3-disubstituted *cyclo*hexanes;[8] although this reversal indicates the diequatorial structure for the *cis*-diamine, some degree of stabilisation of the diaxial structure would result from intramolecular hydrogen bonding, which has been shown to exist in *cis-cyclo*hexane-1 : 3-diol.[9] The existence of the diaxial form in aqueous solution appears to be precluded by the similarity of the pK_{a_1} values for the *cis*- (10·36) and *trans*-diamine (10·30). The somewhat larger difference between the pK_{a_2} values (*cis* 8·54, *trans* 8·29) is in agreement with the greater separation, and therefore stabilisation, of the charges possible for the diprotonated amine in the diequatorial conformation.

Experimental

cis- and *trans*-Hexahydro*iso*phthalic acid, and solutions of hydrazoic acid, were prepared as described previously.[5]

cis-1 : 3-*Diamino*cyclo*hexane*.—A 7·7% solution of hydrazoic acid in chloroform (130 ml.) was added dropwise (3 hr.) to a stirred mixture, at 40°, of chloroform (100 ml.) and a solution of *cis*-hexahydro*iso*phthalic acid (15 g.) in concentrated sulphuric acid (45 ml.). Stirring was continued at 50° for a further 4 hr., evolution of nitrogen having then practically ceased. Evaporation of the chloroform layer left no residue. After dilution with iced water, and cooling, the acid layer was basified with aqueous sodium hydroxide and continuously extracted with two successive portions of chloroform, carbon dioxide being excluded. Removal of the chloroform from the dried (K_2CO_3) extracts through a small fractionating column left a residue from which the volatile material (4·5 g.) was distilled under reduced pressure. Redistillation at atmospheric

[6] Skita and Berendt, *Ber.*, 1919, **52**, 1533.
[7] Caronna, *Gazzetta*, 1941, **71**, 189.
[8] Von Auwers and Schmelzer, *Sitzungsber. Ges. Beförd Naturwiss. Marburg*, 1927, **62**, 113; Pitzer *et al.*, *J. Amer. Chem. Soc.*, **1947**, **69**, 977, 2488; Rossini and Spitzer, *Science*, 1947, **105**, 647.
[9] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492.

pressure afforded a fraction, b. p. 197—198°, and a final distillation gave the diamine (3·9 g.), b. p. 46—48°/0·1 mm., d_4^{20} 0·9515, n_D^{20} 1·4911, $[R_L]_D$ 34·73 (calc. for 1 : 3-diamino*cyclo*hexane, 34·55).

The method employed by Merling [2] gave the diacetyl derivative, needles, m. p. 263° (Found : C, 61·0; H, 9·3; N, 14·4. Calc. for $C_{10}H_{18}O_2N_2$: C, 60·6; H, 9·2; N, 14·1%). Addition of the diamine to *p*-nitrobenzoyl chloride in pyridine gave a very insoluble product, which was lixiviated with successive portions of water, dilute hydrochloric acid, dilute aqueous sodium hydroxide, water, and chloroform. Recrystallisation from acetone gave the *di*-p-*nitrobenzoyl derivative* as needles, m. p. 329—330° (Found : C, 58·3; H, 4·8; N, 13·5. $C_{20}H_{20}O_6N_4$ requires C, 58·3; H, 4·9; N, 13·6%). Addition of the diamine to hot, aqueous picric acid, and recrystallisation of the product from water, gave the *dipicrate monohydrate* as yellow plates, m. p. (corr.) 275° (decomp.) (Found : C, 36·8; H, 3·8; N, 18·9. $C_{18}H_{20}O_{14}N_8,H_2O$ requires C, 36·7; H, 3·8; N, 19·0%), unaffected during 3 hr. at 100°/0·01 mm. The *dihydrochloride*, prepared in chloroform, was obtained after recrystallisation from 95% ethanol as plates, m. p. >360° (Found : C, 38·8; H, 8·6; Cl, 38·1. $C_6H_{14}N_2Cl_2$ requires C, 38·5; H, 8·6; Cl, 37·9%).

trans-1 : 3-*Diaminocyclohexane.*—The method employed for the *cis*-epimer, applied to *trans*-hexahydroisophthalic acid, gave a similar yield of *trans*-1 : 3-diamino*cyclo*hexane, b. p. 197—198°/760 mm., 46—48°/0·1 mm., d_4^{20} 0·9652, n_D^{20} 1·4957, $[R_L]_D$ 34·51.

The *diacetyl derivative*, obtained only after removal of the acetic anhydride, crystallised from acetone as prisms, m. p. 220—221° (Found : C, 61·0; H, 9·1; N, 14·2%). The *di*-p-*nitrobenzoyl derivative*, worked up in the usual manner, was purified by chromatography on alumina. Elution with benzene–chloroform (2 : 1), followed by recrystallisation from acetone–hexane, gave prisms, m. p. 240—241° (Found : C, 58·1; H, 5·1; N, 13·4%). The *dipicrate* crystallised from water as yellow needles, m. p. (corr.) 269° (decomp.) (Found : C, 38·1; H, 3·8; N, 19·5. $C_{18}H_{20}O_{14}N_8$ requires C, 37·8; H, 3·5; N, 19·6%), depressed to 261° on admixture with the *cis*-epimer. The *dihydrochloride* crystallised from 95% ethanol as prisms, m. p. 330° (decomp.) (Found : C, 38·8; H, 8·6; Cl, 37·9%).

Curtius Reaction of cis-*Dimethyl Hexahydroisophthalate.*—The dihydrazide, m. p. 270—272°, was converted through the diazide into the diethylurethane,[1] m. p. 146—147°, and the *dibenzylurethane*, which crystallised from benzene as needles, m. p. 189—190° (Found : C, 69·2; H, 6·8; N, 7·6. $C_{22}H_{26}O_4N_2$ requires C, 69·1; H, 6·9; N, 7·3%).

The latter (1 g.) and W7 Raney nickel (0·5 g.) were shaken for 3 hr. in ethanol with hydrogen at 70°/1000 lb. per sq. in. When cool, the filtered solution was treated with concentrated hydrochloric acid (3 ml.) and evaporated to dryness *in vacuo*. The crystalline residue (0·45 g.) was dissolved in dilute aqueous sodium hydroxide, and the solution filtered, and continuously extracted with chloroform. Removal of the chloroform from the dried extract afforded *cis*-1 : 3-diamino*cyclo*hexane, identified as the dipicrate and diacetyl derivative.

Curtius Reaction of trans-*Dimethyl Hexahydroisophthalate.*—The dihydrazide, m. p. 125—126°, recrystallised from dry methanol–ether (cf. Skita and Rössler [1]), was converted through the diazide into the diethylurethane, m. p. 146—147°, depressed to 113—114° on admixture with the *cis*-epimer, and the dibenzylurethane, which crystallised from aqueous methanol as prisms, m. p. 126·5—127·5° (Found : C, 69·6; H, 6·7; N, 7·6%). Crystallisation of the latter from benzene–hexane gave needles, m. p. 108°, which on admixture with the higher-melting isomorph had m. p. 126—127°. When seeded with prisms a solution of the needles deposited prisms, m. p. 126·5—127·5°.

Hydrogenolysis of the dibenzylurethane was carried out as described for the *cis*-epimer, in similar yield. The product was identified as *trans*-1 : 3-diamino*cyclo*hexane by the dipicrate and diacetyl derivative.

Hydrolysis of the diethylurethane was carried out as described by Skita and Rössler [1] except that the diamine was isolated by extraction with chloroform, and identified as the *trans*-epimer, as before.

Reduction of Dihydroresorcinol Dioxime.—Dihydroresorcinol dioxime (2·1 g.) was hydrogenated in acetic acid under atmospheric conditions with platinum oxide (0·4 g.). Although half of the necessary hydrogen was absorbed in 0·5 hr. the remainder required 14 hr. The bulk of the acetic acid was removed from the filtered solution, which was then basified and continuously extracted with chloroform, giving a diamine (1·3 g.), b. p. 186—190°, n_D^{25} 1·4923. A solution of the derived crude picrate, m. p. 258—260°, in the minimum quantity of boiling water was allowed to cool to 30° and then filtered. The residue (plates) after one recrystallisation from water was identified as pure *cis*-1 : 3-diamino*cyclo*hexane dipicrate (1·2 g.). The filtrate on further cooling deposited needles, which afforded the pure *trans*-epimer (0·2 g.) after three

recrystallisations from water. Evaporation of the mother-liquors left the mixed picrates (0·1 g.).

A solution of the crude acetyl derivative (0·56 g.) from the crude diamine, in hot ethanol (1 ml.), was treated with ethyl acetate (30 ml.), allowed to cool, and filtered. The residue after two similar recrystallisations was identified as the pure *cis*-diacetyl derivative (0·26 g.). Evaporation of the filtrate left material which was identified after two recrystallisations from acetone as the pure *trans*-epimer (0·035 g.).

Hydrogenation of NN'-Diacetyl-m-phenylenediamine.—This substance (10 g.), recrystallised several times from aqueous ethanol, was hydrogenated at 200°/1000 lb. per sq. in. over platinum oxide. After filtration, removal of the acetic acid left a crystalline residue, which was separated into *cis*- (4·6 g.) and *trans-NN'*-diacetyl-1 : 3-diamino*cyclo*hexane (1·9 g.) as described above.

Hydrolysis of these acetyl derivatives was accomplished by boiling concentrated hydrochloric acid in 4 hr. Removal of the acid left the hydrochlorides from which the diamines (*cis*-, n_D^{20} 1·4911; *trans*-, n_D^{20} 1·4962) were obtained in the usual manner.

2 : 4-*Diaza*bicyclo[3 : 3 : 1]*nonan*-3-*one.*—The *cis*-diamine (0·5 g.) and diethyl carbonate (0·5 g.) were heated together in a sealed tube at 200° for 8 hr. The material (0·1 g.) which separated was recrystallised from methanol–ether, yielding 2 : 4-*diaza*bicyclo[3 : 3 : 1]*nonan*-3-*one* as prisms, m. p. 315—316° (Found: C, 60·5; H, 8·3. $C_7H_{12}ON_2$ requires C, 60·0; H, 8·6%). Similar treatment of the *trans*-diamine gave a viscous liquid from which resins were separated. When heated under reflux with carbonyl chloride in water–toluene, the *cis*-diamine yielded its hydrochloride. A similar result occurred in chloroform at 0° in the presence of triethylamine. Only the diethylurethane and the diamine hydrochloride were obtained by reaction with ethyl chloroformate under these conditions. No identifiable product resulted from reaction of the *cis*-diamine and urea by the method of Mulvaney and Evans.[10] Application of hydrazoic acid (2 mols.) to the anhydride of *cis*-hexahydro*iso*phthalic acid as described previously, gave no neutral material but yielded the diamine (15%) (identified as the picrate) and the amino-acid (50%, isolated as the benzoyl derivative).

pK_a *Values.*—Apparent pK_a values were determined by potentiometric titration with standard hydrochloric acid of decinormal solutions of the diamines under nitrogen in a thermostat at 25°.

We are grateful to Professor A. Killen Macbeth for his interest. Microanalyses were carried out at the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

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[10] Mulvaney and Evans, *Ind. Eng. Chem.*, 1948, **40**, 393.

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172. *The Preparation of Some* iso*Quinoline Derivatives.*

By M. S. GIBSON.

The picrates of 3 : 5-, 4 : 5-, 5 : 6-, 5 : 7-, and 5 : 8-dimethyl*iso*quinolines, required as reference substances, have been synthesised by standard methods.

DURING an investigation of gelsemine,[1] it became necessary to prepare as reference samples the picrates of the *x* : 5-dimethyl*iso*quinolines, of which only the 1 : 5-dimethyl compound was known.[2] The desired substances have been prepared by the Bischler–Napieralski reaction.

Condensing propylene oxide with *o*-tolylmagnesium bromide[3] gave only a poor yield of *o*-2-hydroxypropyltoluene and the isolation *via* the hydrogen phthalate was tedious. Accordingly, the desired carbon skeleton was constructed by Reformatsky condensation of *o*-tolualdehyde with ethyl α-bromopropionate, followed by dehydration of the hydroxy-ester, hydrolysis, and reduction to α-methyl-β-*o*-tolylpropionic acid. Degradation of the

[1] Gibson and Robinson, *Chem. and Ind.*, 1951, 93.
[2] Späth, Berger, and Kuntara, *Ber.*, 1930, **63**, 134.
[3] Cf. Levene and Walti, *J. Biol. Chem.*, 1931, **90**, 81.

amide of this acid with sodium hypochlorite under rather specific conditions gave the desired amine.

The phenethylamines required for the remaining syntheses were prepared by catalytic hydrogenation of the corresponding benzyl cyanides, that for 2-*o*-tolylpropylamine being prepared by direct methylation of *o*-xylyl cyanide with methyl iodide and potassamide in liquid ammonia, those for the remainder from the corresponding benzyl chlorides and potassium cyanide.

Each of the phenethylamines was converted into the formyl derivative, which was dehydrated with phosphoric anhydride in boiling tetralin. Dehydrogenation of the resulting dihydro*iso*quinolines gave the *iso*quinolines, which were characterised as picrates.

3-Methyl*iso*quinoline has also been prepared by the Bischler–Napieralski reaction; this route constitutes a more convenient preparation than the earlier method from *o*-cyanobenzyl cyanide.[4]

Experimental

Commercial tetralin was purified by washing it with concentrated sulphuric acid until the washings were only slightly discoloured. The hydrocarbon was then washed with water, dried, and distilled from phosphoric anhydride, the fraction of b. p. 210—212° being collected.

o-2-*Hydroxypropyltoluene.*—A solution of propylene oxide (7 g.) in ether (40 c.c.) was added to a stirred ice-cold solution of the Grignard reagent from *o*-bromotoluene (21 g.) and magnesium (3·2 g.) in ether (80 c.c.). After 12 hr., ice-cold hydrochloric acid was added to the mixture, and the products were isolated by means of ether. Fractionation afforded a considerable quantity of low-boiling material, and then material (5 g.), b. p. 125—150°/17 mm., which was heated in pyridine (9 c.c.) with phthalic anhydride (5 g.) on the steam-bath for 45 min. The resulting solution was poured on crushed ice, acidified, and extracted with chloroform. After being washed, the extract was evaporated, and the residue was treated with sodium carbonate solution. Oily impurites were removed by washing the residue with ether, and the alkaline solution was then acidified and extracted with ether. Evaporation afforded a pale yellow oil (4 g.), which solidified on trituration with light petroleum. Crystallisation from ether gave the *hydrogen phthalate* as cubes, m. p. 127—129° (Found : C, 72·4; H, 6·0. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%). This ester (3 g.) was warmed with 10% sodium hydroxide solution (10 c.c.) for 20 min., yielding o-2-*hydroxypropyltoluene*, b. p. 139—142°/16 mm., n_D^{18} 1·5260 (Found : C, 79·9; H, 9·5. $C_{10}H_{14}O$ requires C, 80·0; H, 9·3%).

Ethyl β-*Hydroxy*-α-*methyl*-β-o-*tolylpropionate.*—Ethyl orthoformate (100 g.) was added with shaking to a cooled solution of the Grignard reagent from *o*-bromotoluene (107 g.) and magnesium (16 g.) in ether (300 c.c.). The mixture was refluxed for 6 hr., cooled, decomposed with sulphuric acid (750 c.c., 10%), and distilled in steam. *o*-Tolualdehyde (42 g.), collected by means of ether, was obtained as an oil, b. p. 94—96°/15 mm.

A solution of the aldehyde (11·2 g.) and ethyl α-bromopropionate (17 g.) in dry benzene (24 c.c.) was added to zinc turnings (6·2 g.) and benzene (8 c.c.) so that the mixture just boiled. After boiling for a further 2 hr., the complex was decomposed with sulphuric acid. *Ethyl* β-*hydroxy*-α-*methyl*-β-o-*tolylpropionate* (11 g.) was obtained as an oil, b. p. 160—162°/16 mm., n_D^{14} 1·5082 (Found : C, 70·2; H, 8·3. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%).

Ethyl α-*Methyl*-β-o-*tolylacrylate.*—Phosphoric anhydride (10 g.) was added during 2 hr. to a solution of the hydroxy-ester (11 g.) in boiling benzene (50 c.c.). After a further hour, the liquid was decanted, and the residue was extracted with hot benzene (2 × 30 c.c.), the extracts being added to the main solution, which was then treated with potassium carbonate (2 g.) to remove traces of phosphoric acid. Distillation afforded the *acrylate* (6 g.) as a yellow oil, b. p. 127—129°/15 mm., n_D^{14} 1·5361 (Found : C, 76·8; H, 8·1. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%).

α-*Methyl*-β-o-*tolylacrylic Acid.*—A solution of the unsaturated ester (5·8 g.) and potassium hydroxide (2 g.) in aqueous ethanol was boiled for 2 hr. Crystallised from water, the *acid* (4·3 g.) formed thread-like needles, m. p. 99—100° (Found : C, 75·1; H, 6·7. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·8%).

α-*Methyl*-β-o-*tolylpropionic Acid.*—The unsaturated acid (4 g.), in sodium carbonate solution, was shaken with 5% palladised barium sulphate (250 mg.) and hydrogen until absorption ceased (90 min.). Isolation by acidification and extraction with ether gave α-*methyl*-β-o-*tolylpropionic*

[4] Gabriel and Neumann, *Ber.*, 1892, **25**, 3563.

acid (3·8 g.), b. p. 112—114°/0·12 mm., n_D^{14} 1·5211 (Found : C, 74·4; H, 8·0. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%).

The *amide* separated from aqueous ethanol in plates, m. p. 112° (Found : C, 74·5; H, 8·4; N, 7·7. $C_{11}H_{15}ON$ requires C, 74·5; H, 8·5; N, 7·9%).

Hofmann Degradation of α-Methyl-β-o-tolylpropionamide.—Chlorine, from potassium permanganate (4·1 g.) and concentrated hydrochloric acid, was passed into cold 10% aqueous sodium hydroxide (250 c.c.), and the amide (10 g.) was added to the resulting solution with shaking. The mixture was gradually heated to 70—80°, and kept at that temperature for an hour. Sodium hydroxide (50 g.) was then added, and the mixture was heated on the steam-bath for 5 hr. When cool, the liquid was extracted with ether, and the extract was dried and saturated with dry hydrogen chloride. The precipitated *o-2-aminopropyltoluene hydrochloride* (3·8 g.) was purified by crystallisation from ether–ethanol, from which it separated as colourless needles, m. p. 166—167° (Found : C, 64·3; H, 8·6; N, 7·8. $C_{10}H_{16}NCl$ requires C, 64·7; H, 8·6; N, 7·6%).

The *picrate* crystallised from aqueous ethanol in yellow needles, m. p. 162—163° (Found : C, 51·2; H, 5·0; N, 14·6. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8; N, 14·8%).

Addition of a few drops of aqueous sodium carbonate solution to a solution of sodium nitroprusside and the free base in aqueous acetone produced a purple colour which slowly faded to pale yellow.

3 : 4-Dihydro-3 : 5-dimethylisoquinoline Picrate.—95% Formic acid (4 c.c.) was heated with *o*-2-aminopropyltoluene (from the hydrochloride, 3·4 g.) at 140—150° for 4 hr. in an open flask. The formyl derivative was dissolved in tetralin (80 c.c.), and phosphoric anhydride (15 g.) was added to the boiling solution during 30—40 min. When the mixture was cool, an excess of hydrochloric acid was added, and tetralin was removed in steam. The residue was strongly basified and again distilled in steam. Isolated by extraction with ether and precipitation with picric acid, *3 : 4-dihydro-3 : 5-dimethylisoquinoline picrate* (900 mg.) crystallised from acetone in yellow needles, m. p. 166—168° (Found : C, 52·4; H, 4·1; N, 14·6. $C_{17}H_{16}O_7N_4$ requires C, 52·6; H, 4·1; N, 14·3%).

3 : 5-Dimethylisoquinoline Picrate.—3 : 5-Dimethyl-3 : 4-dihydro*iso*quinoline, regenerated from the picrate (400 mg.), was heated with 30% palladised charcoal (200 mg.) at 220° for 30 min. The residue was extracted with warm dilute hydrochloric acid; addition of aqueous picric acid precipitated *3 : 5-dimethylisoquinoline picrate* (350 mg.), which separated from ethanol as pale yellow needles, m. p. 219—220° (Found : C, 53·0; H, 3·7; N, 14·5. $C_{17}H_{14}O_7N_4$ requires C, 52·9; H, 3·7; N, 14·5%).

α-o-Tolylpropionitrile.—A solution of *o*-xylyl cyanide[5] (20 g.) in ether (60 c.c.) was added to a stirred solution of potassamide (from potassium, 6 g.) in liquid ammonia (400 c.c.). A solution of methyl iodide (22 g.) in ether (50 c.c.) was then cautiously added. When the ammonia had evaporated, ethanol (10 c.c.) and then water were added. Fractionation of ether-soluble material furnished *α-o-tolylpropionitrile* (15 g.), b. p. 150—152°/20 mm. (Found : C, 82·4; H, 7·6; N, 9·8. $C_{10}H_{11}N$ requires C, 82·8; H, 7·6; N, 9·6%).

α-o-Tolylpropionamide crystallised from aqueous ethanol in needles, m. p. 125—126° (Found : C, 73·7; H, 8·1; N, 8·5. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0; N, 8·6%).

Under analogous conditions, methylation of benzyl cyanide (20 g.) gave α-phenylpropionitrile (16 g.), b. p. 114—116°/13 mm. (Found : C, 82·4; H, 6·9. Calc. for C_9H_9N : C, 82·4; H, 6·9%).

β-o-Tolylpropylamine.—*α-o*-Tolylpropionitrile (9 g.) in ethanol (100 c.c.), saturated with ammonia at 0°, was hydrogenated at 100°/80—100/atm. in the presence of Raney nickel. The *β-o*-tolylpropylamine (8 g.) obtained, b. p. 117—120°/15 mm., yielded a *picrate*, yellow needles (from aqueous methanol), m. p. 175—176° (Found : C, 51·0; H, 4·7; N, 15·1. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8; N, 14·8%). In the sodium nitroprusside test described above, the base gave a fine violet colour, which slowly faded to yellow.

4 : 5-Dimethylisoquinoline Picrate.—Boiling 95% formic acid (7 c.c.) converted the above amine (6 g.) into the formyl derivative which was dehydrated with phosphoric anhydride (27 g.) in boiling tetralin (110 c.c.). As it gave a gummy picrate, the crude dihydro*iso*quinoline was dehydrogenated with 30% palladised charcoal (400 mg.) at 200—220° for 30 min. *4 : 5-Dimethylisoquinoline picrate* (800 mg.) separated from acetone in yellow needles, m. p. 234—235° (Found : C, 52·6; H, 3·9; N, 14·4%).

2 : 3-Dimethylbenzyl Cyanide.—A solution of 2 : 3-dimethylbenzyl chloride[6] (21 g.) and

[5] Atkinson and Thorpe, *J.*, 1907, 1687.
[6] Smith and Spillane, *J. Amer. Chem. Soc.*, 1940, **62**, 2639.

potassium cyanide (15 g.) in aqueous ethanol was boiled for 4 hr. The *nitrile* (14 g.), b. p. 136—144°/17 mm., crystallised from ether in rhombs, m. p. 55—56° (Found: C, 82·8; H, 7·6. $C_{10}H_{11}N$ requires C, 82·8; H, 7·6%).

The nitrile (0·5 g.) was hydrolysed by boiling aqueous-ethanolic potassium hydroxide (0·4 g.) for 6 hr. 2 : 3-*Dimethylphenylacetic acid* (0·4 g.) crystallised from aqueous ethanol in plates, m. p. 113—114° (Found: C, 73·0; H, 7·2. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%).

2 : 3-*Dimethylphenethylamine.*—Reduced as was 1-*o*-tolylpropionitrile, 2 : 3-dimethylbenzyl cyanide (8 g.) yielded 2 : 3-*dimethylphenethylamine* (7 g.), b. p. 116—118°/17 mm. The *picrate* crystallised from aqueous ethanol in yellow needles, m. p. 219—220° (decomp.) (Found: C, 50·8; H, 4·6; N, 14·9. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8; N, 14·8%). The 3 : 5-*dinitrobenzoate* crystallised from aqueous ethanol in needles, m. p. 182—183° (Found: C, 56·6; H, 5·1. $C_{17}H_{19}O_6N_3$ requires C, 56·5; H, 5·3%). The sodium nitroprusside colour was intense magenta, which faded to pale yellow.

5 : 6-*Dimethylisoquinoline Picrate.*—The amide, from the above amine (5 g.) and 98—100% formic acid (6 c.c.) was dehydrated with phosphoric anhydride (25 g.) in tetralin (100 c.c.). 3 : 4-*Dihydro*-5 : 6-*dimethylisoquinoline picrate* (1·5 g.) separated from ethanol in yellow platelets, m. p. 199—200° (Found: C, 52·9; H, 4·1; N, 13·9%). Obtained as in the previous cases, 5 : 6-*dimethylisoquinoline picrate* (950 mg.; from 1·1 g.) formed pale yellow needles (from ethanol), m. p. 246° (decomp.) (Found: C, 52·5; H, 3·7; N, 14·6%).

2 : 4-*Dimethylphenethylamine.*—Reduction of 2 : 4-dimethylbenzyl cyanide[7] (12 g.) under the conditions employed for the 2 : 3-isomer afforded 2 : 4-dimethylphenethylamine (10 g.), b. p. 116—122°/16 mm. The *hydrochloride* crystallised from ethyl acetate–ethanol in needles, m. p. 172—173° (Found: C, 64·6; H, 8·9; N, 7·4. $C_{10}H_{16}NCl$ requires C, 64·7; H, 8·6; N, 7·6%), and the 3 : 5-*dinitrobenzoate* from aqueous ethanol in needles, m. p. 181—182° (Found: C, 56·4; H, 5·1; N, 11·6. $C_{17}H_{19}O_6N_3$ requires C, 56·5; H, 5·3; N, 11·6%).

In the sodium nitroprusside test, the base gave a deep magenta colour, which finally faded to pale yellow.

5 : 7-*Dimethylisoquinoline Picrate.*—The above base (5 g.) was formylated, and the product was dehydrated with phosphoric anhydride in boiling tetralin. 3 : 4-*Dihydro*-5 : 7-*dimethylisoquinoline picrate* (1·1 g.) crystallised from ethanol in yellow needles, m. p. 222—224° (Found: C, 52·9; H, 4·0; N, 14·4%).

Obtained as in the earlier cases, 5 : 7-*dimethylisoquinoline picrate* (650 mg.; from 750 mg.) crystallised from ethanol in yellow needles, m. p. 261—262° (decomp.) (Found: C, 53·0; H, 3·7; N, 14·5%).

2 : 5-*Dimethylphenethylamine.*—2 : 5-Dimethylbenzyl cyanide[8] (11 g.) was reduced under the same conditions as the 2 : 3-isomer to give the amine (9 g.), b. p. 110—112°/13 mm., whose *picrate* crystallised from aqueous ethanol in yellow needles, m. p. 169—170° (Found: C, 50·8; H, 4·8; N, 15·1. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8; N, 14·8%). The *hydrogen oxalate* separated from aqueous ethanol in needles, m. p. 199—200° (Found: C, 60·4; H, 7·2; N, 5·9. $C_{13}H_{17}O_4N$ requires C, 60·3; H, 7·1; N, 5·9%). The sodium nitroprusside colour was intense plum-red which passed through purple to pale yellow.

5 : 8-*Dimethylisoquinoline Picrate.*—The formyl derivative of the above base (5 g.) was dehydrated with phosphoric anhydride (23 g.) in tetralin (100 c.c.). 3 : 4-*Dihydro*-5 : 8-*dimethylisoquinoline picrate* (1·4 g.) separated from acetone in yellow columns, m. p. 182—183° (Found: C, 52·5; H, 4·0; N, 14·2%).

Prepared in the usual manner, 5 : 8-*dimethylisoquinoline picrate* (720 mg.; from 850 mg.) crystallised from ethanol in yellow needles, m. p. 231—233° (decomp.) (Found: C, 53·1; H, 3·9; N, 14·6%).

2′-*Formamidopropylbenzene.*—Crystallised ammonium formate (19 g.) was slowly distilled until the internal temperature reached 165°. Phenylacetone[9] (10 g.) was added and the temperature was raised during 3 hr. to 185—190°. After a further hour at 190°, the mixture was poured into water and extracted with benzene. The amide (7 g.) was obtained as an oil, b. p. 119—121°/0·12 mm. (Found: C, 73·5; H, 8·1; N, 8·5. Calc. for $C_{10}H_{13}ON$: C, 73·6; H, 8·0; N, 8·6%).

3-*Methylisoquinoline Picrate.*—The amide (4 g.) was dehydrated with phosphoric anhydride (20 g.) in tetralin (90 c.c.). 3 : 4-*Dihydro*-3-*methylisoquinoline picrate* (1 g.) crystallised from

[7] Bogert and Stamatoff, *Rec. Trav. chim.*, 1933, **52**, 584.
[8] Bardhan and Sengupta, *J.*, 1932, 2520.
[9] Magidson and Garkusha, *J. Gen. Chem.* (*U.S.S.R.*), 1941, **11**, 339.

ethanol in yellow platelets, m. p. 139—141° (Found : C, 51·5; H, 3·9; N, 15·2. $C_{16}H_{14}O_7N_4$ requires C, 51·3; H, 3·8; N, 15·0%).

3-Methyl*iso*quinoline picrate (430 mg.; from 500 mg.) separated from ethanol in yellow needles, m. p. 197—198° (Found : C, 51·9; H, 3·3; N, 14·8. Calc. for $C_{16}H_{12}O_7N_4$: C, 51·6; H, 3·2; N, 15·0%). Gabriel and Neumann [4] give m. p. 197—198°.

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173. *Some Basic Esters of 9-Xanthenylacetic Acid.*

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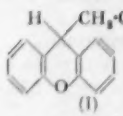
Some basic esters and the corresponding quaternary salts of 9-xanthenylacetic acid (I; R = H) have been prepared for study as spasmolytic agents. In addition, the 2- and 4-methyl, and the 4-methoxy-derivative of methantheline bromide (II) have been prepared.

9-Xanthenylacetic acid was obtained by Fosse [1] by condensation of xanthhydrol with malonic acid in pyridine. The condensation proceeds equally smoothly with alkylmalonic acids, α-9-xanthenylpropionic, α-9-xanthenylbutyric, and β-phenyl-α-9-xanthenylpropionic



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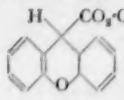

(II)

acid being prepared in this way. The acids were esterified either by reaction with the dialkylaminoethyl halide in propan-2-ol [2] or by conversion into the acid chlorides, followed by reaction with excess of the basic alcohol in benzene. Quaternisation with methyl bromide was carried out in acetone at −10°, and with the other alkyl bromides in a sealed tube at 100°.

2- and 4-Methyl- and 2-methoxy-xanthone were reduced with sodium and ethanol, and the resulting xanthens carboxylated by treating the lithium derivatives with carbon dioxide. The position of carboxylation was proved in each case by oxidation to the original xanthone with chromium trioxide in acetic acid. The xanthen-9-carboxylic acids so obtained were esterified and quaternised in the usual way, to give the 2- and 4-methyl- and 2-methoxy-derivative of the salt (II).

Experimental

The esters described below were prepared by the acid chloride route unless otherwise stated.

α-9-*Xanthenylpropionic Acid.*—A solution of xanthhydrol (4 g.) and methylmalonic acid (2 g.) in pyridine (10 ml.) was heated at 60° for 2 hr., at 80° for 30 min., and finally boiled for 1 hr. The pyridine was evaporated under reduced pressure and the residue dissolved in ether. The acid was extracted with sodium carbonate solution, precipitated with dilute hydrochloric acid, and recrystallised from light petroleum (b. p. 60—80°). α-9-*Xanthenylpropionic acid* formed plates, m. p. 122° (Found : C, 75·3; H, 5·6. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

α-9-*Xanthenylbutyric acid* separated in cubes, m. p. 114—116° (Found : C, 76·0; H, 6·2. $C_{17}H_{16}O_3$ required C, 76·1; H, 6·0%), from light petroleum (b. p. 80—100°).

β-*Phenyl*-α-9-*xanthenylpropionic acid* formed plates, m. p. 165° (Found : C, 79·6; H, 5·2. $C_{22}H_{18}O_3$ requires C, 80·0; H, 5·5%), from light petroleum (b. p. 60—80°).

2-*Diethylaminoethyl* α-9-*Xanthenylbutyrate Hydrochloride.*—α-9-Xanthenylbutyric acid (5 g.), 2-diethylaminoethyl chloride (3·5 g.), and dry propan-2-ol (50 ml.) were boiled for 4 hr. The

[1] Fosse, *Bull. Soc. chim. France*, 1906, **35**, 1005.
[2] Horenstein and Pahlicke, *Ber.*, 1938, **71**, 1654.

solvent was removed under reduced pressure and the residue treated with sodium carbonate solution and ether. The ethereal layer was washed, dried and evaporated and the product precipitated with ethanolic hydrogen chloride. The *ester hydrochloride* (5 g.) formed plates, m. p. 166° (Found: C, 68·9; H, 7·7; N, 3·8; Cl, 8·7. $C_{22}H_{29}O_3N,HCl$ requires C, 68·4; H, 7·4; N, 3·5; Cl, 8·8%), after crystallisation from ethanol–ether. The *methobromide* crystallised from propan-2-ol–ether in needles, m. p. 158° (Found: C, 61·7; H, 6·8; N, 3·3. $C_{24}H_{32}O_3NBr,\frac{1}{2}H_2O$ requires C, 61·3; H, 6·8; N, 3·0%).

2-Diethylaminoethyl β-Phenyl-α-9-xanthenylpropionate Hydrochloride.—The corresponding acid (5 g.) was heated under reflux in benzene with purified thionyl chloride (5 g.). After 45 min. the solvent was removed under reduced pressure and the residue re-evaporated twice with dry toluene. The acid chloride was dissolved in benzene (50 ml.) and 2-diethylaminoethanol (5 ml.) added, after which the mixture was refluxed for 4 hr. The hydrochloride was decomposed with sodium carbonate solution and the benzene washed thoroughly with water to remove diethylaminoethanol. The *product* (5·3 g.) was precipitated with ethanolic hydrogen chloride and recrystallised from methanol–ethyl acetate, to give needles, m. p. 169° (Found: C, 70·1; H, 7·1; N, 3·3. $C_{27}H_{31}O_3N,HCl,\frac{1}{2}H_2O$ requires C, 70·1; H, 7·2; N, 3·0%). The *methobromide* formed needles, m. p. 177—180° (Found: C, 64·4; H, 7·0; N, 3·1. $C_{28}H_{34}O_3NBr,\frac{1}{2}H_2O$ requires C, 64·5; H, 7·0; N, 2·7%), after crystallisation from propan-2-ol–ether.

2-Methylxanthen.—2-Methylxanthone (3 g.), dissolved in boiling ethanol (60 ml.), was treated with sodium (7 g.) added as rapidly as possible. Then the ethanol was removed in steam and the residue recrystallised from aqueous alcohol and then from light petroleum (b. p. 40—60°). *2-Methylxanthen* (2·1 g.) separated in plates, m. p. 98° (Found: C, 86·0; H, 6·3. $C_{14}H_{12}O$ requires C, 85·7; H, 6·1%).

4-Methylxanthen crystallised from alcohol in prismatic rods, m. p. 40° (Found: C, 85·4; H, 6·2%). *2-Methoxyxanthen* formed needles, m. p. 70° (Found: C, 78·7; H, 5·7. $C_{14}H_{12}O_2$ requires C, 79·3; H, 5·7%), on crystallisation from light petroleum (b. p. 40—60°).

2-Methylxanthen-9-carboxylic Acid.—A solution of butyl-lithium, prepared from lithium (5 g.), *n*-butyl bromide (60 g.), and dry ether (600 ml.) under nitrogen, was treated with 2-methylxanthene (25 g.), in portions. After the vigorous evolution of butane had ceased, the solution was refluxed for 3 hr., allowed to cool and then poured on dry, powdered carbon dioxide. Next day water and ether were added, and the aqueous layer was acidified. *2-Methylxanthen-9-carboxylic acid* (20·5 g.) formed needles, m. p. 198—199° (Found: C, 75·2; H, 5·3. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%), from benzene–light petroleum.

Esters of 9-xanthenylacetic acid.

			Found (%)			Required (%)		
R *	M. p. or b. p.	Formula	C	H	N	C	H	N
·CH_2·CH_2·NMe_2,HCl	158°	$C_{19}H_{21}O_3N,HCl$	65·3	6·3	3·8	65·6	6·43	4·0
·CH_2·CH_2·NMe_3}Br	225	$C_{20}H_{24}O_3NBr$ [a]	59·2	6·1	3·3	59·1	5·9	3·3
·CH_2·CH_2·NMe_2Et}Br	135	$C_{21}H_{26}O_3NBr,\frac{1}{2}H_2O$	59·0	6·3	3·5	58·7	6·3	3·3
·CH_2·CH_2·NMe_2Pr^n}Br	125	$C_{22}H_{28}O_3NBr$	60·6	6·5	3·0	60·8	6·5	3·2
·CH_2·CH_2·NMe_2Pr^i}Br	145	$C_{22}H_{28}O_3NBr,H_2O$	58·4	5·9	3·1	58·4	6·4	3·1
·CH_2·CH_2·NEt_2,HCl	140	$C_{21}H_{25}O_3N,HCl$	66·9	6·9	3·3	67·4	6·7	3·7
·CH_2·CH_2·$NMeEt_2$}Br	158	$C_{22}H_{28}O_3NBr$	60·4	6·9	3·1	60·8	6·5	3·2
·CH_2·CH_2·NEt_3}Br	125	$C_{23}H_{30}O_3NBr$ [b]	—	—	3·2	—	—	3·1
·CH_2·CH_2·NEt_2Pr^n}Br	130	$C_{24}H_{32}O_3NBr,\frac{1}{2}H_2O$	61·1	6·7	3·1	61·2	7·0	3·0
·CH_2·CH_2·NEt_2Pr^i}Br	165	$C_{24}H_{32}O_3NBr,\frac{1}{2}H_2O$	61·1	6·8	3·0	61·2	7·0	3·0
·CH_2·CH_2·NPr^n_3	160°/0·05 mm.	$C_{25}H_{29}O_3N$	75·2	8·0	3·7	75·2	7·9	3·8
·CH_2·CH_2·$NMePr^n_2$}Br	138—139	$C_{24}H_{32}O_3NBr$	62·0	7·6	3·0	62·3	6·9	3·0
·CH_2·CH_2·$NEtPr^n_2$}Br	158	$C_{25}H_{34}O_3NBr$ [c]	—	—	2·9	—	—	2·9
·CH_2·$CH_2NPr^n_2$}Br	113—115	$C_{24}H_{32}O_3NBr$	63·7	7·3	3·6	63·7	7·3	2·9
·CH_2·CH_2·NPr^i_2,HCl	130	$C_{23}H_{29}O_3N,HCl,\frac{1}{2}H_2O$	66·4	7·0	4·6	66·9	7·5	3·4
·CH_2·CH_2·NC_5H_{10},HCl	168	$C_{23}H_{25}O_3N,HCl$	67·8	6·8	6·4	68·1	6·7	3·6
·CH_2·CH_2·$NMeC_5H_{10}$}Br	98	$C_{23}H_{28}O_3NBr,2H_2O$	57·6	6·6	3·2	57·3	6·6	2·9
·CH_2·CH_2·NC_4H_8O,HCl	158	$C_{21}H_{23}O_4N,HCl$	64·9	6·0	3·7	64·7	6·1	3·6
·CH_2·CH_2·$NMeC_4H_8O$}Br	195	$C_{23}H_{26}O_4NBr$	58·8	5·9	3·2	59·1	5·8	3·1
·CH_2·$CHMe$·NEt_2	180°/0·1 mm.	$C_{23}H_{27}O_2N$	75·2	8·0	3·7	74·8	7·6	4·0
·CH_2·$CHMe$·$NMeEt_2$}Br	148	$C_{23}H_{30}O_3NBr$	61·4	6·9	2·9	61·6	6·7	3·2
·CH_2·CH_2·CH_2·NEt_2	180°/0·3 mm.	$C_{23}H_{27}O_2N$	74·6	7·6	3·7	74·8	7·6	4·0
·CH_2·CH_2·CH_2·$NMeEt_2$}Br	98—101	$C_{23}H_{30}O_3NBr$	59·3	6·8	3·0	59·5	6·9	3·0
·CH_2·$CHMe$·NC_5H_{10},HCl	197	$C_{23}H_{27}O_2N,HCl$	68·3	7·0	3·5	68·7	6·7	3·5
·CH_2·$CHMe$·$NMeC_5H_{13}$}Br	93—94	$C_{24}H_{30}O_3NBr,H_2O$	59·7	7·5	2·9	59·4	6·7	2·9

* ·NC_5H_{10} = piperidino; ·NC_4H_8O = morpholino.
[a] Found: Br, 19·9. Reqd.: Br, 19·7%. [b] Found: Br, 18·0. Reqd.: Br, 17·9%. [c] Found: Br, 17·1. Reqd.: Br, 16·8%.

4-Methylxanthen-9-carboxylic acid formed needles, m. p. 202—203° (Found: C, 74·8; H, 5·1%), from benzene. *2-Methoxyxanthen-9-carboxylic acid* crystallised from benzene and alcohol in needles, m. p. 203—204° (Found: C, 70·7; H, 4·8. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

2-Diethylaminoethyl 2-methylxanthen-9-carboxylate (prepared by Horenstein and Pahlicke's method [2]) distilled as a pale yellow oil, b. p. 160°/0·2 mm. (Found: C, 74·1; H, 7·6; N, 4·0. $C_{21}H_{25}O_3N$ requires C, 74·3; H, 7·4; N, 4·1%). The *methobromide* formed hygroscopic plates, m. p. 137—138° (Found: N, 3·3; Br, 18·5. $C_{22}H_{28}O_3NBr$ requires N, 3·2; Br, 18·4%), from propan-2-ol–ether. The *ethobromide* formed hygroscopic cubes, m. p. 153—154° (Found: N, 2·9; Br, 17·2. $C_{23}H_{30}O_3NBr \cdot H_2O$ requires N, 3·0; Br, 17·2%), on similar crystallisation.

2-Diethylaminoethyl 4-methylxanthen-9-carboxylate (prepared by Horenstein and Pahlicke's method [2]) had b. p. 152°/0·1 mm. (Found: C, 73·7; H, 7·5; N, 4·2. $C_{21}H_{25}O_3N$ requires C, 74·3; H, 7·4; N, 4·1%). The *methobromide* formed cubes, m. p. 182—183° (Found: N, 3·2; Br, 18·0. $C_{22}H_{28}O_3NBr$ requires N, 3·2; Br, 18·4%), from propan-2-ol–ether.

Diethyl-2-(2′-methoxy-9′-xanthoyl)ethylmethylammonium bromide formed prisms, m. p. 172—173° (Found: 3·2; Br, 18·4. $C_{23}H_{28}O_4NBr$ requires N, 3·1; Br, 17·7%), on similar crystallisation.

Other *esters* are recorded in the Table.

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174. *The Synthesis of Glucosamine 6-(Dihydrogen Phosphate).*

By J. M. Anderson and Elizabeth Percival.

A crystalline monohydrate of glucosamine 6-(dihydrogen phosphate) has been synthesised from glucosamine *via* 1 : 3 : 4-tri-*O*-acetyl-*N*-acetyl-β-D-glucosamine. All the intermediate derivatives prepared were crystalline and were characterised. Periodate oxidation confirmed the structure of the 6-phosphate.

Brown [1] records the phosphorylation of glucosamine by hexokinase and the isolation of a small quantity of glucosamine 6-phosphate. He considers that the process may be important in the series of anabolic stages whereby naturally occurring polysaccharides containing glucosamine residues are produced. More recently Leloir and Cardini [2] isolated enzymes from the mould, *Neurospora crassa*, which catalyse the change of hexose 6-phosphate into glucosamine 6-phosphate in the presence of glutamine and of acetylglucosamine 1-phosphate into the corresponding 6-phosphate. This led Kalckar and Klenow [3] to suggest that "the formation of glucosamine 6-phosphate should also be considered as a pathway in the biosynthesis of purine ribosides, the more so since the nitrogen of the *N*-ribosidic linkage in purine ribosides is derived specifically from the amide nitrogen of glutamine." In view of the wide interest in this derivative of glucosamine it appeared to us that an authentic synthesis, whereby supplies of this derivative might be available for more extensive enzymic studies, was desirable.

Direct phosphorylation of glucosamine led to an impure product.[4] In order to prepare glucosamine 6-phosphate from glucosamine it is necessary first to protect the secondary hydroxyl groups and the amino-group with other residues. Preliminary experiments were carried out on crystalline *N*-*p*-methoxybenzylidene-D-glucosamine. It was hoped to prepare 1 : 3 : 4-tri-*O*-acetyl-*N*-*p*-methoxybenzylidene-6-*O*-triphenylmethyl-D-glucosamine and, after removal of the triphenylmethyl residue, to phosphorylate the product. Unfortunately attempts to prepare crystalline derivatives were unsuccessful and these experiments were abandoned. The conditions necessary for the hydrolysis of *O*-acetyl and *N*-acetyl groups in glucosamine were studied, and, as these did not appear to be likely

[1] Brown, *Biochim. Biophys. Acta*, 1951, **7**, 487.
[2] Leloir and Cardini, *Biochim. Biophys. Acta*, 1953, **12**, 15.
[3] Kalckar and Klenow, *Ann. Review Biochem.*, 1954, **23**, 574.
[4] Anderson and Percival, *Chem. and Ind.*, 1954, 1018.

to cause the removal of a 6-phosphate group, a synthesis was begun with 1 : 3 : 4-tri-*O*-acetyl-*N*-acetyl-6-*O*-triphenylmethyl-D-glucosamine as intermediate.

Crystalline *N*-acetyl-D-glucosamine was prepared, and after tritylation and acetylation 1 : 3 : 4-tri-*O*-acetyl-*N*-acetyl-6-*O*-triphenylmethyl-β-D-glucosamine with carbon tetrachloride of crystallisation was isolated in 25% yield. From the mother-liquors 5·5% of the α-anomer with mixed solvent of crystallisation was obtained. Further treatment of the mother-liquors gave 2% of 3 : 4-di-*O*-acetyl-*N*-acetyl-1 : 6-di-*O*-triphenylmethyl-D-glucosamine. The phenomenon of solvent of crystallisation is seldom encountered in non-ionic sugar derivatives. Triphenylmethyl ethers, however, appear to be more liable than most derivatives to behave in this way. For example, the preparation of an ethanol solvate of triphenylmethyldulcitol has been reported [5] and Edington, Hirst, and Percival [6] isolated methyl tri-*O*-benzoyl-6-*O*-triphenylmethyl-α-mannopyranoside with various solvents of crystallisation.

When acetic acid at 100° was used to remove the triphenylmethyl residues from the tetra-acetates [7] hydrolysis of the 1-acetyl group also occurred, but by treatment of the β-acetate with a cold saturated solution of hydrogen bromide in glacial acetic acid for not longer than 60 seconds crystalline 1 : 3 : 4-tri-*O*-acetyl-*N*-acetyl-β-D-glucosamine was obtained in 67% yield. This product could not be isolated by the method used for 1 : 2 : 3 : 4-tetra-acetyl-β-D-glucose.[8] The three times greater solubility of the tetra-acetyl-β-D-glucosamine in water than in chloroform made it necessary to employ exhaustive chloroform extraction and to eliminate the usual water washing of the extract.

In view of the larger yield of the β-anomer of the triphenylmethyl ether, and the fact that all attempts to isolate crystalline 1 : 3 : 4-tri-*O*-acetyl-*N*-acetyl-α-D-glucosamine were unsuccessful the synthesis was continued in the β-series. As the possibility of acetyl migration [9] during the removal of the triphenylmethyl group could not be ignored the structure of the 1 : 3 : 4-tri-*O*-acetyl-*N*-acetyl-β-D-glucosamine was confirmed by reconversion into the 6-triphenylmethyl ether, and by toluene-*p*-sulphonylation followed by the replacement of the toluene-*p*-sulphonyl group by iodine under the standard conditions for the replacement of a primary toluene-*p*-sulphonyloxy-group.[10]

Phosphorylation of the tetra-acetyl-β-D-glucosamine was carried out with diphenyl phosphorochloridate and crystalline 1 : 3 : 4-tri-*O*-acetyl-*N*-acetyl-β-D-glucosamine 6-(diphenyl phosphate) was isolated in 70% yield. Hydrogenolysis of the phenyl groups gave a good yield of the crystalline 6-(dihydrogen phosphate). The acetyl groups were hydrolysed with sulphuric acid and a barium salt was precipitated by ethanol after neutralisation of the hydrolysate with barium carbonate. The difficulty of converting all the phosphate into the barium salt combined with that of removing all the inorganic barium salts made the isolation of a pure salt difficult. Exact neutralisation of the sulphuric acid hydrolysate with barium hydroxide led to the crystallisation of the monohydrate of D-glucosamine 6-(dihydrogen phosphate). In addition a small yield of a crystalline dihydrate was isolated on autohydrolysis of the tetra-acetyl phosphoric acid derivative. Chromatographic analysis of the free acid and of the barium salt (after removal of barium) showed identical spots.

The constitution of the dihydrogen phosphate and of the barium salt was confirmed by periodate oxidation :[11] both took up the theoretical quantity of periodate (Table 1) and gave no formaldehyde (Table 2) :

TABLE 1. *Uptake of periodate in moles/mole of sugar.*

Time (hr.)	22	64	94	Theor.
Glucosamine hydrochloride	4·8	4·9	4·9	5
Glucosamine 6-(barium phosphate)	3·8	3·9	3·9	4
Glucosamine 6-(dihydrogen phosphate)	3·9	3·9	3·9	4

[5] Wolfrom, Burke, and Waisbrot, *J. Amer. Chem. Soc.*, 1939, **61**, 1827.
[6] Edington, Hirst, and Percival, *J.*, 1955, 2281.
[7] Jeanloz, *J. Amer. Chem. Soc.*, 1952, **74**, 4597.
[8] Reynolds and Evans, *Org. Synth.*, 1942, **22**, 56.
[9] Haworth, Hirst, and Teece, *J.*, 1931, 2858; Helferich and Klein, *Annalen*, 1927, **455**, 173.
[10] Tipson, Clapp, and Cretcher, *J. Org. Chem.*, 1947, **12**, 133.

TABLE 2. *Formaldehyde release.*

	Mole of CH_2O/mole of sugar	Theor.
Glucosamine hydrochloride	0·81	1·0
N-Acetyl-α-D-glucosamine	0·98	1·0
Glucosamine 6-(barium phosphate)	0·00	0·0
Glucosamine 6-(dihydrogen phosphate)	0·00	0·0

Estimation of the glucosamine content of the 6-phosphate by the Elson–Morgan technique gave 98% of glucosamine.

The rate of hydrolysis of the phosphate group was compared with that of glucose 6-phosphate.[11] Whilst glucosamine 6-phosphate was 50% hydrolysed during 73 hours, glucose 6-phosphate had undergone 50% hydrolysis in 23 hours under the same conditions.

EXPERIMENTAL

Solvents were removed under reduced pressure below 50°. M. p.s were determined on the Kofler hot-stage microscope. Optical rotations were determined at 20° ± 2° in $CHCl_3$ unless otherwise stated. Light petroleum was the fraction of b. p. 60—80°.

1 : 3 : 4-*Tri*-O-*acetyl*-N-*acetyl*-6-O-*triphenylmethyl*-D-*glucosamine*.—D-Glucosamine hydrochloride (130 g.) was converted into crystalline *N*-acetyl-α-D-glucosamine (115 g., 96%) by the method of Roseman and Ludowieg.[12] After recrystallisation from aqueous ethanol–ether the crystals had m. p. 209—210° (decomp.), $[\alpha]_D^{18}$ +41° (Found: C, 43·4; H, 6·5; N, 6·9. Calc. for $C_8H_{15}O_6N$: C, 43·4; H, 6·8; N, 6·3%).

N-Acetyl-α-D-glucosamine (75 g.) in dry pyridine (500 ml.) in the presence of "Drierite" (8 g.) was heated with triphenylmethyl chloride (98 g.) at 100° until the reactants had dissolved (20 min.).[13] Acetic anhydride (150 ml.) was added to the hot solution and, after cooling overnight, the mixture was filtered and the excess of triphenylmethyl chloride in the filtrate decomposed with ice-water. The product was isolated as a white amorphous solid by pouring the mixture into vigorously stirred ice-water (3000 ml.). After drying, the product (170 g., 85%) had $[\alpha]_D$ +32° (*c*, 1·1). Solution of the crude product in hot carbon tetrachloride gave, on cooling, colourless needles (68 g.) of the carbon tetrachloride *solvate* of 1 : 3 : 4-*tri*-O-*acetyl*-N-*acetyl*-6-O-*triphenylmethyl*-β-D-*glucosamine*. These crystals lost solvent at 100—110° and had m. p. 187—189°, $[\alpha]_D$ +22° (*c*, 1·4) (Found: C, 52·3; H, 4·7; N, 2·3; Cl, 21·9; loss at 100°/15 mm. in 18 hr., 26·2. $3C_{33}H_{35}O_9N,4CCl_4$ requires C, 51·9; H, 4·4; N, 1·8; Cl, 23·8; CCl_4, 25·8%). The *amine* freed from solvent had m. p. 189—191°, $[\alpha]_D$ +33° (*c*, 1·0) (Found: C, 66·8; H, 5·7; N, 2·0. $C_{33}H_{35}O_9N$ requires C, 67·2; H, 6·0; N, 2·4%). When an ethanolic solution of the crystals was heated with Fehling's solution for several minutes a positive reducing test was obtained.

After removal of the β-anomer, evaporation of the carbon tetrachloride from the mother-liquors gave a syrup, which, on dissolution in warm chloroform and treatment with an equal volume of ether, gave crystals (11·0 g.) of a mixed solvate of 1 : 3 : 4-tri-*O*-acetyl-*N*-acetyl-6-*O*-triphenylmethyl-α-D-glucosamine, m. p. 111—112°, $[\alpha]_D$ +90° (*c*, 0·9) (Found: C, 66·6; H, 6·0; N, 2·6; Cl, 2·7; loss at 100°/15 mm. in 20 hr., 5·6%). Freed from solvent the *amine* had m. p. 154—156°, $[\alpha]_D$ +97° (*c*, 1·2) (Found: C, 66·9; H, 6·0; N, 1·8%). These crystals also reduced Fehling's solution if tested as above.

The residual mother-liquors, when warmed and treated with light petroleum to turbidity, deposited, on cooling, crystals of 3 : 4-*di*-O-*acetyl*-N-*acetyl*-1 : 6-*di*-O-*triphenylmethyl*-D-*glucosamine* (4 g.), m. p. 254—256°, $[\alpha]_D$ −29° (*c*, 1·0), non-reducing to Fehling's solution (Found: C, 75·9; H, 6·0; N, 2·2. $C_{50}H_{49}O_8N$ requires C, 76·0; H, 6·0; N, 1·8%).

3 : 4-*Di*-O-*acetyl*-N-*acetyl*-α-D-*glucosamine*.—To the bistriphenylmethyl ether (1·01 g.) in glacial acetic acid (18 ml.) at 100°, water (12 ml.) was added dropwise and the temperature kept at 100° for 60 min. Cooling, addition of water (60 ml.), filtration, and concentration gave a syrup (390 mg.) which on trituration with chloroform partially crystallised. This 3 : 4-*di*-O-*acetyl*-N-*acetyl*-α-D-*glucosamine* (150 mg., 38%), after recrystallisation from acetone–light petroleum, gave a negative test for the triphenylmethyl group[14] and had m. p. 186—187°, $[\alpha]_D$ +75° (*c*, 0·9), $[\alpha]_D^{18}$ +65° (5 min., *c*, 1·0 in H_2O) → +35° (8 hr., const.) (Found: C, 47·2; H, 6·3; N, 4·5. $C_{12}H_{19}O_8N$ requires C, 47·2; H, 6·3; N, 4·6%).

[11] Robison, *Biochem. J.*, 1932, **26**, 2191.
[12] Roseman and Ludowieg, *J. Amer. Chem. Soc.*, 1954, **76**, 301.
[13] Helferich and Klein, *Annalen*, 1926, **450**, 219.
[14] Valentin, *Coll. Czech. Chem. Comm.*, 1931, **3**, 499.

1 : 3 : 4-*Tri*-O-*acetyl*-N-*acetyl*-β-D-*glucosamine*.—In the following experiments the carbon tetrachloride solvate of the triphenylmethyl ether was used.

(*a*) Treatment as in the previous experiment with glacial acetic acid (36 ml.) of **1 : 3 : 4**-tri-*O*-acetyl-*N*-acetyl-6-*O*-triphenylmethyl-β-D-glucosamine (2·0 g.) gave a syrup (800 mg.), whose cooled solution in ethanol gave crystals of **3 : 4**-di-*O*-acetyl-*N*-acetyl-α-D-glucosamine (330 mg., 43%), which on recrystallisation from ethanol had m. p. and mixed m. p. 188—189°, $[\alpha]_D^{19}$ +68° (5 min., *c*, 1·0 in H_2O) → +32° (8 hr., const.) (Found : C, 47·1; H, 6·2; N, 4·7%).

(*b*) A cooled solution of the β-monotriphenylmethyl ether (10 g.) in acetic acid (32 ml.) was shaken with a cooled saturated solution of hydrogen bromide in acetic acid (3·2 ml.) with cooling for 60 sec. The precipitated triphenylmethyl bromide was removed and the filtrate poured into ice-water (200 ml.). This liquid mixture and the washings (300 ml.) from the bromide were extracted with chloroform (8 × 300 ml.). The extracts were dried without washing and on concentration gave a syrup. Residual chloroform and acetic acid were removed by repeated distillation with dry toluene. A crystalline residue (2·9 g., 67%), m. p. 169—171°, was obtained. After two recrystallisations from chloroform–ether, these crystals of **1 : 3 : 4-*tri*-O-*acetyl*-N-*acetyl*-β-D-*glucosamine*** had m. p. 175—176°, $[\alpha]_D^{18}$ +5·5° (*c*, 1·6), $[\alpha]_D^{18}$ +18° (*c*, 1·1 in H_2O) (Found : C, 48·1; H, 6·2; N, 4·0. $C_{14}H_{21}O_9N$ requires C, 48·4; H, 6·1; N, 4·0%).

Triphenylmethylation of **1 : 3 : 4-*Tri*-O-*acetyl*-N-*acetyl*-β-D-*glucosamine*.**—The foregoing β-tetra-acetate (200 mg.) and triphenylmethyl chloride (160 mg., 1 mol.) in pyridine (2 ml.) at 50° (60 hr.) in the presence of " Drierite " gave, after the usual treatment, the carbon tetrachloride solvate of **1 : 3 : 4**-tri-*O*-acetyl-*N*-acetyl-6-*O*-triphenylmethyl-β-D-glucosamine as needles (150 mg., 33%), $[\alpha]_D$ +24° (*c*, 1·2). The crystals lost solvent at 100—110° and the desolvated material had m. p. and mixed m. p. with the specimen previously prepared 185—187°.

1 : 3 : 4-*Tri*-O-*acetyl*-N-*acetyl*-6-O-*toluene*-p-*sulphonyl*-β-D-*glucosamine*.—A solution of **1 : 3 : 4**-tri-*O*-acetyl-*N*-acetyl-β-D-glucosamine (100 mg.) and toluene-*p*-sulphonyl chloride (110 mg., 2 mol.) in pyridine (1 ml.) in the presence of " Drierite " at room temperature (72 hr.) gave a syrup (105 mg.) which crystallised under methanol. **1 : 3 : 4-*Tri*-O-*acetyl*-N-*acetyl*-6-O-*toluene*-p-*sulphonyl*-β-D-*glucosamine*** had m. p. 170—171°, $[\alpha]_D$ +16° (*c*, 1·1) (Found : C, 50·7; H, 5·4; S, 6·1. $C_{21}H_{27}O_{11}NS$ requires C, 50·3; H, 5·4; S, 6·4%).

This material (10 mg.) was heated in a sealed tube with sodium iodide (10 mg.) in acetone at 100° for 2 hr.[16] The mixture deposited characteristic plate-shaped crystals of sodium toluene-*p*-sulphonate.

1 : 3 : 4-*Tri*-O-*acetyl*-N-*acetyl*-β-D-*glucosamine* 6-(*Diphenyl Phosphate*).—**1 : 3 : 4**-Tri-*O*-acetyl-*N*-acetyl-β-D-glucosamine (11 g.) in dry pyridine (45 ml.) in the presence of " Drierite " at 0° was treated with diphenyl phosphorochloridate[15] (9·35 g., 1·1 mol.) with shaking and cooling during 20 min. The mixture was kept at 0° for a further 15 min.[15] and, after being kept overnight at 10°, was cooled to 0° and filtered. Excess of acid chloride was decomposed by a few drops of ice-water and the mixture kept at room temperature for 30 min. Slow pouring into ice-water with stirring gave a gel which quickly changed to a white crystalline solid. This on recrystallisation from aqueous acetone gave **1 : 3 : 4-*tri*-O-*acetyl*-N-*acetyl*-β-D-*glucosamine* 6-(*diphenyl phosphate*)** (11·8 g.), m. p. 144—145°, $[\alpha]_D$ +25° (*c*, 0·7) (Found : C, 53·6; H, 5·3; N, 2·7; P, 5·4. $C_{26}H_{30}O_{12}NP$ requires C, 53·9; H, 5·2; N, 2·4; P, 5·3%). Extraction of the aqueous filtrate with chloroform (2 × 250 ml.) and thorough washing of the extracts yielded on removal of the chloroform a syrup. On trituration with aqueous acetone this gave a further crop of the same crystals (1·1 g.).

1 : 3 : 4-*Tri*-O-*acetyl*-N-*acetyl*-β-D-*glucosamine* 6-(*Dihydrogen Phosphate*).—The diphenyl ester (12·6 g.) (in 3 experiments of 4·2 g. each) in aldehyde-free ethanol (total, 100 ml.) was refluxed for 25 min. with activated charcoal (3·0 g.). The charcoal was removed and the solution added to ethanol (10 ml.) containing the platinum catalyst (from 0·33 g. of Adams platinum oxide reduced *in situ* for each experiment). The solution was shaken in hydrogen at slightly >1 atm. Uptake stopped at 7·6 mol. (95%) in 18, 19, and 7 hr. severally for the 3 experiments. Removal of the solvent at 25° gave a syrup which on trituration with ethanol deposited crystals (7·09 g., 75%) of **1 : 3 : 4-*tri*-O-*acetyl*-N-*acetyl*-β-D-*glucosamine* 6-(*dihydrogen phosphate*)**, m. p. 166—168° (decomp.), $[\alpha]_D^{19}$ +25° (*c*, 1·0 in H_2O) (Found : C, 38·9; H, 5·0; N, 3·6; P, 7·0. $C_{14}H_{22}O_{12}NP$ requires C, 39·3; H, 5·2; N, 3·3; P, 7·3%).

D-*Glucosamine* **6-(*Dihydrogen Phosphate*).**—(a) *Barium salt.* **1 : 3 : 4**-Tri-*O*-acetyl-*N*-acetyl-β-D-glucosamine 6-(dihydrogen phosphate) (400 mg.) was hydrolysed with N-sulphuric acid

[15] Foster, Overend, and Stacey, *J.*, 1951, 980.
[16] Lardy and Fischer, *J. Biol. Chem.*, 1946, **164**, 513.

(12 ml.) at 100° until the rotation was constant (2·5 hr.) {$[\alpha]_D^{20}$ +60° (*c*, 2·0 in N-H_2SO_4) for the dipolar ion of the product}. The solution was shaken overnight with finely divided barium carbonate, then filtered, and the barium salts were washed with water. The combined filtrates were treated with ethanol (4 vol.). A white powder was precipitated which was washed with 90% aqueous ethanol, ethanol–ether (3 : 1, then 1 : 3), and ether. The dried precipitate (290 mg.; P, 6·3%) was treated in 0·01N-hydrochloric acid (6 ml.) with ethanol (24 ml.). The precipitate (150 mg., 41%) had $[\alpha]_D^{18}$ (dipolar ion) +53° (*c*, 0·3 in H_2O; pH 2·5). {Brown [17] records $[\alpha]_D^{24}$ +48·5° (*c*, 0·5 in H_2O; pH 2·5)} (Found: C, 19·6; H, 4·4; N, 4·7; total P, 7·8; inorg. P, 0·05. Calc. for $C_6H_{12}O_8NPBa$: C, 18·3; H, 3·1; N, 3·6; total P, 7·9%).

(b) *Free acid.* (i) 1 : 3 : 4-Tri-*O*-acetyl-*N*-acetyl-β-D-glucosamine 6-(dihydrogen phosphate) (2·8 g.) was hydrolysed with N-sulphuric acid as before. The solution was neutralised with a half-saturated solution of barium hydroxide, samples (1 drop) being tested for barium with a solution of rhodizonic acid [18] in water (when all the sulphuric acid had been precipitated a red-brown precipitate of barium rhodizonate was formed). After removal of the barium sulphate by centrifugation the clear solution (pH 4) was concentrated to 50 ml. Addition of ethanol to turbidity gave crystals of the *acid* (0·81 g., 45%) after several days at 0°. This, after drying at 18°/0·1 mm., had m. p. 170—180° (decomp.), $[\alpha]_D$ +54° (*c*, 0·5 of the hydrate in H_2O) (Calc. for the anhyd. compound, +58°) (Found: C, 25·8; H, 5·7; N, 5·2; total P, 11·3; inorg. P, 0·0. $C_8H_{14}O_8NP,H_2O$ requires C, 26·0; H, 5·8; N, 5·1; P, 11·2%).

(ii) A solution of 1 : 3 : 4-tri-*O*-acetyl-*N*-acetyl-β-D-glucosamine 6-(dihydrogen phosphate) (200 mg.) in water (3 ml.) was heated at 100° for 30 hr. Decolorisation with charcoal and concentration gave a glass which on dissolution in water (4 ml.), addition of alcohol, and nucleation with the crystalline monohydrate of D-glucosamine 6-(dihydrogen phosphate) gave crystals (17 mg.) of a dihydrate. These had m. p. 165—175° (decomp.) (Found: C, 24·4; H 6·0; N, 4·6; P, 10·4. $C_8H_{14}O_8NP,2H_2O$ requires C, 24·4; H, 6·1; N, 4·7; P, 10·5%).

Chromatography by the ascending technique [19] with ethyl acetate–pyridine–formamide (6 : 1 : 3) as eluate and ferric chloride–sulphosalicylic acid spray,[20] gave a single identical spot for the glucosamine 6-(dihydrogen phosphate) applied in dilute sulphuric acid solution and the barium salt (freed from barium with sulphuric acid).

Oxidation by Periodate.—(a) *Periodate uptake.* Oxidations were carried out on glucosamine 6-(barium phosphate) and 6-(dihydrogen phosphate) and glucosamine hydrochloride.[1] The weighed substance (100—200 μ moles) was dissolved in water, the solution adjusted to pH 4·5, and the volume made up to 25 ml. A sample (6 ml.) was treated with 3 ml. of 0·1M-sodium metaperiodate, made up to 10 ml. with distilled water, and set aside in the dark at room temperature. At suitable intervals, portions (3 ml.) were treated with sodium hydrogen carbonate (0·6 g.), potassium iodide (0·6 g.), and sodium arsenite (0·1N; 5 ml.). After 10 min. the mixture was titrated with 0·05N-iodine. Barium was removed from the barium salt by the addition of sulphuric acid (0·1N; 3 ml.) before adjustment of the pH to 4·5.

(b) *Formaldehyde release.* Solutions of the sugar derivatives (0·7 μ mole/ml.) were oxidised in buffered solution (pH 7·5, sodium carbonate) with periodate for 21 hr. and the formaldehyde released was estimated under the conditions advocated by O'Dea and Gibbons.[21] Three glucose solutions of different concentrations were used as standards, and the filter used was the Ilford spectrum yellow (606).

Elson–Morgan Estimation of Glucosamine Content.—The glucosamine content of the 6-phosphate was estimated according to the method of Elson and Morgan [22] as modified by Belcher, Nutten, and Sambrook.[23] Glucosamine solutions were used as standards, and measurements made with the Ilford spectrum green (604) filter. The crystalline monohydrate of glucosamine 6-(dihydrogen phosphate) was found to have 98% of its theoretical glucosamine content. The optical densities of the coloured solutions from glucosamine hydrochloride and the 6-(di hydrogen phosphate) (each 0·05 μg. of glucosamine per ml.) were examined at 450—600 mμ with a Unicam SP600 spectrophotometer. It was found necessary to use 2-cm. cells to obtain optical densities equivalent to those Belcher and his co-workers [23] describe for 2-mm. cells, and, although the colours from glucosamine and the 6-phosphate appeared identical to the eye, when the optical

[17] Brown, *J. Biol. Chem.*, 1953, **204**, 877.
[18] Feigl, "Spot Tests," Vol. I, Elsevier, 1954, p. 203.
[19] Horne and Pollard, *J. Bact.*, 1948, **55**, 231.
[20] Wade and Morgan, *Nature*, 1953, **171**, 529.
[21] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.
[22] Elson and Morgan, *ibid.*, 1933, **27**, 1824.
[23] Belcher, Nutten, and Sambrook, *Analyst*, 1954, **79**, 201.

densities were plotted against the wavelength there was a slight displacement (512 to 518 mμ) in the position of the maximum together with a minor difference in the shape of the curve. This may be due to the production of two similar chromophores in each case, but in rather different quantities.

Hydrolysis of D-*Glucosamine* 6-(*Dihydrogen Phosphate*).—The crystalline monohydrate of glucosamine 6-(dihydrogen phosphate) (67·9 mg.) in N-hydrochloric acid (25 ml.) was heated at 100° and aliquot parts were analysed at suitable times for hydrolysed phosphorus. Robison [11] carried out an identical hydrolysis of glucose 6-phosphate and his figures are given in the Table for comparison.

Time (hr.)	0	4	8	20	45	70	80
Phosphorus (mg./ml.)	0	0·013	0·021	0·047	0·104	—	0·160
Hydrolysis (%) :							
Glucosamine 6-dihydrogen phosphate	0	4·3	6·8	15·6	34·2	—	52·6
Glucose 6-phosphate [11]	—	12·7	21·6	44·9	75·0	88·9	—

Hydrolysis of 1 : 3 : 4 : 6-*Tetra*-O-*acetyl*-N-*acetyl- and* N-*Acetyl-glucosamine.*—4% Solutions were hydrolysed with N-hydrochloric acid at 100° and the hydrolyses followed polarimetrically. (*a*) Tetra-*O*-acetyl-*N*-acetyl-β-D-glucosamine: α_D +1·99° (2 min); +1·36° (42 min.); +1·43° (57 mins.); +1·43° (70 min.). Crystalline D-glucosamine hydrochloride (84%), $[\alpha]_D^{18}$ +86° (3 min.) ⟶ +70° (const.) (*c*, 1·5 in H_2O), was recovered from the hydrolysate. (*b*) *N*-Acetyl-α-D-glucosamine: α_D +1·42° (initial); +2·65 (2 hr.); +2·65° (3 hr.).

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175. *The Ammonolysis of Methyl* 2 : 3-*Anhydro*-D-*furanosides. Part II.* Methyl* 2 : 3-*Anhydro*-5-O-*methyl*-α- *and* -β-D-*lyxofuranosides.*

By J. M. ANDERSON and ELIZABETH PERCIVAL.

Ammonolyses of methyl 2 : 3-anhydro-5-*O*-methyl-α- and -β-D-lyxofuranosides led to the isolation of crystalline derivatives of methyl 3-amino-3-deoxy-5-*O*-methyl-α- and -β-D-arabinosides. During this work methyl 2-acetamido-2-deoxy-β-D-xylofuranoside, 3-acetamido-3-deoxy-2-*O*-methyl-β-D-arabofuranoside, and 3-acetamido-3-deoxy-2 : 5-*O*-dimethyl-α- and -β-D-arabinosides and two new derivatives of methyl D-xylofuranoside have been prepared.

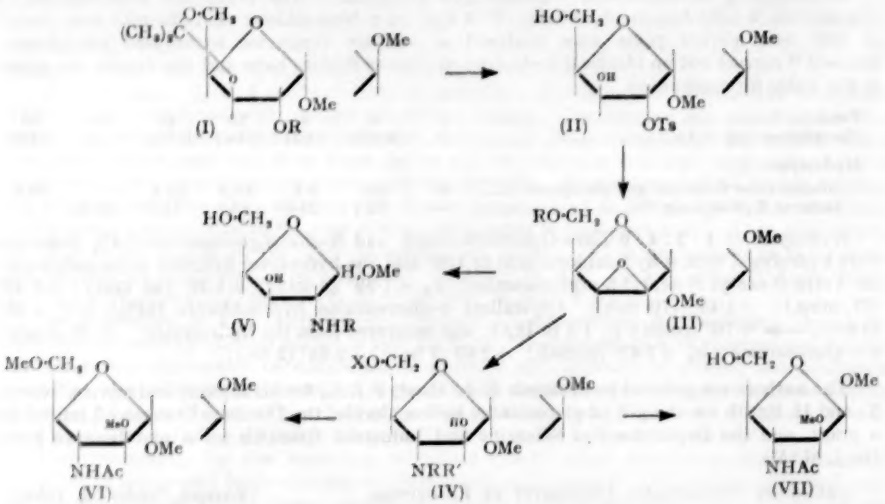
PERCIVAL and ZOBRIST [1] reported the synthesis of methyl 2 : 3-anhydro-α-D-lyxofuranoside (III; R = H) from a mixture of methyl 3 : 5-*O*-*iso*propylidene-α- and -β-D-xylofuranosides (I; R = H) by tosylation (I; R = Ts), mild acid hydrolysis (II), and alkaline hydrolysis of the tosyl residue. Subsequently Baker, Schaub, and Williams,[2] from a similar synthesis, isolated the β-anomer of the 2 : 3-anhydro-sugar (III; R = H), after first partly separating methyl 3 : 5-*O*-*iso*propylidene-αβ-D-xylofuranoside into its two anomers by distillation. Although these authors carried out the subsequent syntheses separately on the two fractions and isolated crystalline methyl 2 : 3-anhydro-α- and -β-D-lyxofuranosides, none of their intermediate derivatives was obtained crystalline. During the present work fractional distillation of the *iso*propylidene-αβ-xylofuranoside led to the separation of two fractions, whose specific rotations differed considerably from the values recorded by Baker and his co-workers. That the present separation was more efficient was confirmed by the ready isolation of the two crystalline methyl 3 : 5-*O*-*iso*propylidene-2-*O*-toluene-*p*-sulphonyl-D-xylofuranosides (I; R = Ts). Hydrolysis of the *iso*propylidene group with boiling

* Part I, Anderson and Percival, *J.*, 1955, 1042.

[1] Percival and Zobrist, *J.*, 1953, 564.

[2] Baker, Schaub, and Williams, *J. Amer. Chem. Soc.*, 1955, **77**, 7.

1% methanolic hydrogen chloride [3] or at 50° with 80% acetic acid [2] caused anomerisation; by use of 0·1% methanolic hydrogen chloride at room temperature, however, no anomerisation occurred and crystalline methyl 2-*O*-toluene-*p*-sulphonyl-α-D-xylofuranoside (II) was obtained in excellent yield.



Crystalline methyl 2 : 3-anhydro-α- [1] and -β-lyxofuranosides [2] were prepared and, after ammonolysis followed by treatment with acetone, gave methyl 3-deoxy-3-*iso*propylideneamino-α- and -β-D-arabofuranosides (IV; RR′ = CMe_2, X = H), respectively. The mother liquors were examined for methyl 2-amino-2-deoxyxylofuranoside (V; R = H) derivatives. The *N*-acetyl-3 : 5-*iso*propylidene derivative appeared to be the most appropriate to prepare, but specific *N*-acetylation and attempted condensation with acetone failed to yield any crystalline derivatives from the mother liquors of the α-anomer. The mother liquors of the β-anomer, however, gave crystals (0·6% of the ammonolysis product) which gave correct analytical results for a methyl 2-acetamido-2-deoxyxylofuranoside (V; R = Ac) and were converted into a free sugar hydrochloride whose rotation was identical with that recorded [4] for 2-amino-2-deoxy-D-xylose hydrochloride.

Methylation of both anomers of methyl 3-acetamido-3-deoxy-D-arabofuranoside [5] (IV; R = H, R′ = Ac, X = H) gave the respective crystalline 2 : 5-dimethyl ethers (VI). Complete methylation proved difficult in the β-series; after three treatments two crops of crystals were obtained. The first was shown by chromatography to be a single entity and by analysis to be a methyl 3-acetamido-3-deoxymonomethylarabinoside. Determination of melting point of mixtures showed that it was not the 5-methyl ether, and conversion into a toluene-*p*-sulphonate which showed the presence of a primary toluene-*p*-sulphonyloxy-group [6] proved it to be methyl 3-acetamido-3-deoxy-2-*O*-methyl-β-D-arabofuranoside (VII). The second crop of crystals was shown by paper chromatography and by analysis to be a mixture of mono- and di-methyl ethers. Three further methylations of the mother liquors were necessary before the pure dimethyl ether (VI) could be isolated.

Methylation of both anomers of methyl 2 : 3-anhydro-D-lyxofuranoside (III; R = H) gave crystalline α- and β-5-methyl ethers (III; R = Me) which on ammonolysis and appropriate treatment gave crystalline *N-iso*propylidene and *N*-acetyl derivatives. That these were derivatives of 3-amino-3-deoxy-D-arabinose was proved by the isolation, after

[2] Percival and Zobrist, *J.*, 1952, 4306.
[4] Wolfrom and Anno, *J. Amer. Chem. Soc.*, 1953, **75**, 1038.
[5] Anderson and Percival, *J.*, 1955, 1042.
[6] Tipson, Clapp, and Cretcher, *J. Org. Chem.*, 1947, **12**, 133.

complete methylation, of crystalline dimethyl ethers identical with the 2 : 5-dimethyl ethers (VI) obtained above. No crystalline derivatives of xylose could be isolated from the mother liquors after the removal of the *N-iso*propylidene (α-5-methyl) and *N*-acetyl (β-5-methyl) arabinose derivatives.

Although Baker and his co-workers [2] record sharp melting points and correct analyses for the *N-iso*propylidene derivatives, we were unable, even after repeated recrystallisation, to isolate crystals of pure methyl 3-deoxy-3-*iso*propylideneamino-α- or -β-arabofuranosides (IV; RR′ = CMe_2, X = H) or of the corresponding α-5-methyl ether (IV; R_2 = CMe_2, X = Me). It is thought that the extreme acid-lability of the *iso*propylidene group probably leads to contamination with the amino-sugar.

Cleavage of the epoxide ring in methyl 2 : 3-anhydrolyxofuranosides (III) with ammonia can yield, in theory, 3-amino-3-deoxyarabinose (IV) and 2-amino-2-deoxyxylose (V) derivatives, depending on whether the break occurs between $C_{(3)}$ or $C_{(2)}$ and the oxygen of the ring. In all the derivatives studied, only a very small quantity of a xylose derivative was isolated in a single experiment. Fission of the epoxide ring with ammonia occurred preferentially between $C_{(3)}$ and the attached oxygen atom, the attacking group entering at $C_{(3)}$, since 3-amino-3-deoxyarabinose derivatives were isolated in every experiment. No attempt will be made to explain the reason for this preferential cleavage or the mechanism of fission until work on other epoxide derivatives of furanose sugars has been carried out.

Experimental

Solvents were removed under reduced pressure. Methanolic ammonia was prepared by saturating dry methanol with ammonia at 0°. Light petroleum was the fraction, b. p. 60—80°. The solvent used in chromatographic separation on Whatman No. 1 paper was butanol–ethanol–water (4 : 1 : 5). Chlorine and starch–potassium iodide [7] were used as detecting agent for the amino-compounds. The R_G values were assessed by using tetramethylglucose (R_G 1·0) as standard.

Methyl 3 : 5-O-iso*Propylidene*-2-O-*toluene*-p-*sulphonyl*-α- *and* -β-D-*xylofuranoside*.—Methyl 3 : 5-*O-iso*propylidene-D-xylofuranoside was prepared from D-xylose [1] (200 g.); the crude product was purified by chloroform extraction (3 × 200 ml.) of an aqueous solution (200 ml.). Repeated fractional distillation (fractions of similar specific rotation were combined and refractionated) of the concentrated chloroform extracts (172 g.; in 30 g. portions) through a Vigreux column led finally to the separation of two fractions. Fraction I: 71·6 g. (42%), b. p. 60—70°/0·05 mm., $[\alpha]_D$ +75° (*c*, 1·0 in $CHCl_3$; average: range, +70°—+82°), n_D^{18} 1·4683. Fraction II: 55·2 g. (32%), b. p. 90—100°/0·05 mm., $[\alpha]_D$ −80° (*c*, 1·0 in $CHCl_3$; average: range, −65° to −85°), n_D^{17} 1·4650. Baker *et al.*[2] record for fraction I, $[\alpha]_D^{24}$ +18° in H_2O, and for fraction II, $[\alpha]_D^{24}$ −64° in H_2O.

Methyl 3 : 5-*O-iso*propylidene-D-xylofuranoside (71 g.; $[\alpha]_D$ +75°) was treated in pyridine (120 ml.) with toluene-*p*-sulphonyl chloride (73 g.).[8] A crystalline product (92 g., 74%), m. p. 77°, $[\alpha]_D^{21}$ +66° (*c*, 1·4 in $CHCl_3$), was isolated. After recrystallisation from light petroleum, *methyl* 3 : 5-O-iso*propylidene*-2-O-*toluene*-p-*sulphonyl*-α-D-*xylofuranoside* (I; R = Ts) had m. p. 79—80°, $[\alpha]_D^{18}$ +68° (*c*, 1·1 in $CHCl_3$) (Found: C, 53·2; H, 6·1; S, 8·9. $C_{16}H_{22}O_7S$ requires C, 53·2; H, 6·2; S, 9·0%).

Methyl 3 : 5-*O-iso*propylidene-D-xylofuranoside (55 g.; $[\alpha]_D$ −80°) after similar treatment gave a product (80 g.), $[\alpha]_D^{18}$ −37° (*c*, 1·1 in $CHCl_3$). Recrystallisation from aqueous methanol gave methyl 3 : 5-*O-iso*propylidene-2-*O*-toluene-*p*-sulphonyl-β-D-xylofuranoside (I; R = Ts) (62 g., 64%), m. p. 119—120°, $[\alpha]_D^{17}$ −53° (*c*, 0·9 in $CHCl_3$), $[\alpha]_D^{18}$ −44° (*c*, 0·4 in MeOH). This was identical with the material isolated by Percival and Zobrist [3] from syrupy methyl 3 : 5-*O-iso*propylidene-αβ-D-xylofuranoside.

Methyl 2-O-*Toluene*-p-*sulphonyl*-α- *and* -β-D-*xylofuranosides*.—Methyl 3 : 5-*O-iso*propylidene-2-*O*-toluene-*p*-sulphonyl-α-D-xylofuranoside (89 g.), dissolved in 0·1% methanolic hydrogen chloride (20 ml.), was kept at room temperature until the rotation reached a constant value: α_D +1·46° (initial), +1·95° (5 min.), +2·12 (15 min.), +2·13 (20 min.; const.). After neutralisation with silver carbonate, a syrup (75 g., 95%) was obtained which crystallised completely. Recrystallisation from chloroform–light petroleum gave *methyl* 2-O-*toluene*-p-*sulphonyl*-α-D-*xylofuranoside* (II), m. p. 90—91°, $[\alpha]_D^{25}$ +101° (*c*, 1·3 in $CHCl_3$) (Found: C, 49·5;

[7] Rydon and Smith, *Nature*, 1952, **169**, 922.
[8] Edington, Hirst, and Percival, *J.*, 1955, 2281.

H, 5·8; S, 10·4. $C_{13}H_{16}O_7S$ requires C, 49·1; H, 5·7; S, 10·1%). The β-form was isolated as a syrup (95%), $[\alpha]_D^{22}$ −20° (*c*, 1·0 in $CHCl_3$), n_D^{22} 1·5243.

Attempted Isolation of Xylose Derivatives.—Ammonolysis of methyl 2 : 3-anhydro-α-D-lyxofuranoside (III; R = H) (13·2 g.) by heating it with methanolic ammonia in an autoclave at 120° for 48 hr. gave, after treatment with charcoal, a brown syrup (14·6 g., 99%). This was dissolved in hot acetone (250 ml.);[2] the cooled solution deposited methyl 3-deoxy-3-*iso*propylideneamino-α-D-arabofuranoside (IV; R_2 = CMe_2, X = H). The total yield, after several treatments of the mother liquors, was 15·5 g. (85%). *N*-Acetylation of the residual material (1·8 g., 10%) in water (50 ml.) with methanol (5 ml.), resin (50 ml.), and acetic anhydride (1·25 ml.)[9] gave a syrup (1·5 g., 83%). When shaken with acetone (50 ml.), anhydrous copper sulphate (8 g.), and N-sulphuric acid (0·08 ml.),[2] and then treated appropriately, this yielded a non-reducing syrup (1·0 g.). Fractionation of this between chloroform and water by a counter-current technique gave, from the aqueous fraction, a non-reducing syrup (900 mg., 90%), $[\alpha]_D^{22}$ +112° (*c*, 1·1 in H_2O), which gave a negative iodoform test for the *iso*propylidene group. Paper chromatography showed the presence of two components, having R_G 0·67 and 0·76 (methyl 3-acetamido-3-deoxy-α-D-arabofuranoside has R_G 0·73). The chloroform fraction yielded a non-reducing syrup (40 mg., 4%), which was not examined further.

Methyl 2 : 3-anhydro-β-D-lyxofuranoside (III; R = H) (8·4 g.) gave, after ammonolysis and appropriate treatment, methyl 3-deoxy-3-*iso*propylideneamino-β-D-arabofuranoside (IV; RR′ = CMe_2, X = H) (7·1 g., 62%). The residue (3·5 g.) was *N*-acetylated[9] and the syrupy product (3·4 g., 96%) condensed with dry acetone[2] as above, giving a non-reducing syrup (3·0 g.), $[\alpha]_D^{22}$ −48° (*c*, 1·5 in H_2O), which was fractionated between chloroform and water. The aqueous fraction gave a non-reducing syrup (2·65 g., 88·5%) which after distillation at 170—175°/0·1 mm. (0·94 g.) showed on chromatographic analysis spots with R_G 0·60 and 0·70 (methyl 3-acetamido-3-deoxy-β-D-arabofuranoside has R_G 0·65). A solution of this syrup in ethanol–light petroleum deposited crystals (60 mg.), m. p. 222—224°, $[\alpha]_D^{26}$ −64° (*c*, 0·9 in H_2O), R_G 0·60 (Found: C, 46·4; H, 7·4. $C_9H_{15}O_5N$ requires C, 46·8; H, 7·4%). A solution of the crystals (13·5 mg.) in hydrochloric acid (10 ml.; 3N) was heated at 100° for 30 min. Concentration to dryness gave a syrup (12·2 mg.) which crystallised; the solid had $[\alpha]_D^{15}$ +40° (*c*, 0·60 in H_2O) (Wolfrom and Anno[4] record $[\alpha]_D$ +40° for 2-amino-2-deoxy-D-xylose hydrochloride).

The chloroform fraction yielded a dark brown syrup (70 mg., 2·3%) which was not examined further.

Methyl 3-Acetamido-3-deoxy-2 : 5-di-O-methyl-α- and -β-D-arabofuranosides.—Methyl 3-acetamido-3-deoxy-α-D-arabofuranoside[5] (IV; R = H, R′ = Ac, X = H) (4·0 g.) was methylated four times with methyl iodide (23 ml.) and silver oxide (20 g.). The product, a mobile syrup (4·30 g.), after distillation at 50—120°/0·05 mm., had n_D^{20} 1·4647. This partly crystallised; the hygroscopic crystals (2·69 g., 59%) of *methyl 3-acetamido-3-deoxy-2 : 5-di-O-methyl-α-D-arabofuranoside* (VI) could not be recrystallised. Freed from syrup by cold light petroleum they had m. p. 57—59°, $[\alpha]_D^{23}$ +131° (*c*, 1·0 in H_2O), R_G 0·97 (Found: C, 51·6; H, 8·1; N, 5·8; OMe, 39·2. $C_{10}H_{19}O_5N$ requires C, 51·5; H, 8·2; N, 6·0; OMe, 39·9%).

Methyl 3-acetamido-3-deoxy-β-D-arabofuranoside[5] (IV; R = H, R′ = Ac, X = H) (2·0 g.) in methanol (15 ml.) after three methylations with Purdie's reagents gave a product (0·90 g.), which was dissolved in acetone. Cooling the solution gave crystals *A* (580 mg.). Addition of light petroleum caused the deposition crystals *B* (280 mg.). Crystals *A* were non-reducing and after recrystallisation (acetone) depressed the m. p. of the starting material, crystals *B*, and methyl 3-acetamido-3-deoxy-5-*O*-methyl-β-D-arabofuranoside. The crystals, m. p. 157°, were therefore *methyl 3-acetamido-3-deoxy-2-O-methyl-β-D-arabofuranoside*, $[\alpha]_D^{24}$ −118° (*c*, 0·7 in H_2O), R_G 0·77 (Found: C, 49·7; H, 7·9; N, 6·3; OMe, 28·3. $C_9H_{17}O_5N$ requires C, 49·3; H, 7·8; N, 6·4; OMe, 28·3%). Tosylation[8] (50 mg.) gave a crystalline toluene-*p*-sulphonate (55 mg.), m. p. 85—86°, $[\alpha]_D^{22}$ −69° (*c*, 0·9 in $CHCl_3$), which gave a positive test for a primary toluene-*p*-sulphonyloxy-group.[6]

Crystals *B* were also non-reducing, and after recrystallisation (acetone–light petroleum) had m. p. 156—160° (Found: C, 51·0; H, 8·5; N, 5·0; OMe, 36·2. $C_{10}H_{19}O_5N$ requires C, 51·5; H, 8·2; N, 6·0; OMe, 39·9%). The m. p.s of starting material, crystals *A*, and methyl 3-acetamido-3-deoxy-5-*O*-methyl-β-D-arabofuranoside were all depressed. Chromatographic analysis showed two spots, R_G 0·92 and R_G 0·78.

The residue (1·1 g.; OMe, 24·9%) left after the separation of crystals *A* and *B* was thrice methylated with Purdie's reagents. The product (1·0 g.; OMe, 36·5%) was extracted with

[9] Roseman and Ludowieg, *J. Amer. Chem. Soc.*, 1954, **76**, 301.

cold acetone (2 ml.). Addition of light petroleum gave needles of *methyl 3-acetamido-3-deoxy-2 : 5-di-O-methyl-β-D-arabofuranoside* (VI) (0·51 g.) which after recrystallisation had m. p. 174—175°, $[\alpha]_D^{23}$ −107° (*c*, 0·8 in H_2O), R_G 0·92 (Found: C, 51·6; H, 8·1; N, 5·9; OMe, 39·4. $C_{10}H_{19}O_5N$ requires C, 51·5; H, 8·2; N, 6·0; OMe, 39·9%).

Methyl 2 : 3-Anhydro-5-methyl-β-D-lyxofuranoside.—Methyl 2 : 3-anhydro-β-D-lyxofuranoside [2] (III; R = H) (8·0 g.), initially dissolved in dry methanol (15 ml.), was thrice methylated with Purdie's reagents. The product (7·3 g.), a very mobile syrup, $[\alpha]_D^{26}$ −84° (*c*, 0·7 in H_2O), gave on distillation (b. p. 54—57°/0·05 mm.) a syrup (6·4 g., 73%) which crystallised when cooled to 0° but melted at *ca.* 14—15°. It had $[\alpha]_D^{20}$ −88° (*c*, 1·1 in H_2O), n_D^{21} 1·4470 (Found: C, 52·8; H, 7·8; OMe, 39·1. $C_7H_{12}O_4$ requires C, 52·5; H, 7·6; OMe, 38·8%).

Ammonolysis of Methyl 2 : 3-Anhydro-5-O-methyl-α-D-lyxofuranoside.—A solution of methyl 2 : 3-anhydro-5-*O*-methyl-α-D-lyxofuranoside [1] (III; R = Me) (9·1 g.) in dry methanolic ammonia (500 ml.) was heated in an autoclave at 120° for 48 hr. The resulting brown syrup after filtration and treatment with charcoal was concentrated, and the product freed from ammonia by distillation with ethanol. The residue, a brown syrup (9·51 g., 94%), was dissolved in hot acetone and the solution cooled. Crystals (8·34 g., 72%), shown to be *methyl 3-deoxy-5-O-methyl-3-isopropylideneamino-α-D-arabofuranoside* (IV; RR′ = CMe_2, X = Me), were deposited and after several recrystallisations (acetone) had m. p. 115—125°, $[\alpha]_D^{20}$ +106° (*c*, 0·9 in H_2O) (Found: C, 54·3; H, 9·4; N, 6·4. $C_{10}H_{19}O_4N$ requires C, 55·3; H, 8·8; N, 6·5%). Concentration of the mother liquors gave a dark brown syrup (2·82 g.), $[\alpha]_D$ +65° (*c*, 0·7 in H_2O). Distillation at 100° (bath temp.)/0·03 mm. gave a syrup (520 mg.) from which more (80 mg.) of the crystals were isolated.

The crystalline *N-iso*propylidene derivative (5·81 g.) in water (150 ml.) was acidified with 2N-hydrochloric acid and *N*-acetylated.[9] The syrupy product (5·80 g., 99%) crystallised after distillation at 140°/0·05 mm. All attempts at recrystallisation failed; the hygroscopic *methyl 3-acetamido-3-deoxy-5-O-methyl-α-D-arabofuranoside* (3·87 g.) (IV; R = H, R′ = Ac, X = Me), freed from syrup by ether, had m. p. 60—62°, $[\alpha]_D^{21}$ +119° (*c*, 0·9 in H_2O), R_G 0·88 (Found: C, 48·2; H, 7·6; N, 5·9; OMe, 27·8. $C_9H_{17}O_5N$ requires C, 49·3; H, 7·8; N, 6·4; OMe, 28·3%).

Four methylations with Purdie's reagents gave a mobile syrup (1·07 g. from 1·0 g.), n_D^{23} 1·4548. Distillation gave two fractions: (*a*) 310 mg., b. p. (bath temp.) 80°/0·02 mm., which was not examined further; and (*b*) 520 mg., b. p. 100°/0·02 mm., which crystallised. Recrystallisation was difficult but the crystals were freed from syrup with light petroleum. They had m. p. and mixed m. p. 57—59° with authentic methyl 3-acetamido-3-deoxy-2 : 5-di-*O*-methyl-α-D-arabofuranoside (VI), $[\alpha]_D$ +129° (*c*, 0·9 in H_2O), R_G 0·97 (Found: OMe, 39·1. Calc. for $C_{10}H_{19}O_5N$: OMe, 39·9%).

Ammonolysis of Methyl 2 : 3-Anhydro-5-O-methyl-β-D-lyxofuranoside.—A brown syrup (6·17 g., 90%) was obtained when methyl 2 : 3-anhdyro-5-*O*-methyl-β-D-lyxofuranoside (III; R = Me) (6·2 g.) was treated with methanolic ammonia (500 ml.) under the conditions used for the α-anomer. Attempts to prepare an *N-iso*propylidene [3] derivative gave, after distillation at 84—86°/0·03 mm., a syrup (5·64 g., 74%). *N*-Acetylation [8] gave a syrup (5·44 g., 96%) which on dissolution in acetone and addition of light petroleum deposited crystals (2·66 g., 48%), shown to be *methyl 3-acetamido-3-deoxy-5-O-methyl-β-D-arabofuranoside* (IV; R_2 = H, R′ = Ac, X = Me), m. p. 161—162° after recrystallisation (acetone–light petroleum), $[\alpha]_D^{23}$ −114° (*c*, 1·2 in H_2O), R_G 0·81 (Found: C, 49·5; H, 7·8; N, 5·8; OMe, 28·1. $C_9H_{17}O_5N$ requires C, 49·3; H, 7·8; N, 6·4; OMe, 28·3%).

Evaporation of the mother liquors and distillation gave a syrup (71 mg.), $[\alpha]_D^{20}$ +30° (*c*, 0·7 in H_2O). An aqueous extract of the distillation residues yielded another syrup (80 mg.), $[\alpha]_D^{23}$ +18° (*c*, 0·8 in H_2O).

Methyl 3-acetamido-3-deoxy-5-*O*-methyl-β-D-arabofuranoside (IV; R = H, R′ = Ac, X = Me) (1·0 g.) in methanol (5 ml.) was methylated four times with Purdie's reagents. The product (1·0 g.) was dissolved in acetone and light petroleum added, giving methyl 3-acetamido-3-deoxy-2 : 5-di-*O*-methyl-β-D-arabofuranoside (VI) identical with that synthesised as above. The samples had m. p. and mixed m. p. with authentic material 174—175°, $[\alpha]_D^{23}$ −107° (*c*, 1·1 in H_2O), R_G 0·92 (Found: OMe, 40·1. Calc. for $C_{10}H_{19}O_5N$: OMe, 39·9%.

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176. *Interaction of Boron and Hydrogen Halides with Esters of Boronic Acids.*

By P. B. Brindley, W. Gerrard, and M. F. Lappert.

Boron trifluoride and trichloride, interacting in various proportions with di-*n*-butyl *n*-butylboronate (or di-*n*-butyl phenylboronate) afforded either *n*-butyl(or phenyl)boron dihalides, $BRHal_2$, or the corresponding halogenoboronites, $BRHal{\cdot}OBu^n$, a novel class of organoboron compounds also obtained from the boronates and either *n*-butyl dihalogenoboronites or phenylboron dichloride. Hydrogen chloride rapidly dealkylated di-*tert.*-butyl phenylboronate, but not at all the *n*-, *iso*-, or *sec.*-butyl isomer or di-*n*-butyl *n*-butylboronate. Di-*n*-butyl phenylboronate was slowly dealkylated with hydrogen bromide, as was (+)-di-2-methylheptyl phenylboronate, in this case with preponderant inversion. The reactions are compared with analogous ones of trialkyl borates.

Certain alkyl- and aryl-boronates $[BR(OR')_2]$ have recently been prepared.[1,2] The interactions of boron trifluoride and trichloride, of *n*-butyl difluoro- and dichloro-boronite ($BHal_2{\cdot}OBu^n$), and of hydrogen chloride and bromide with di-*n*-butyl *n*-butylboronate $[BBu^n(OBu^n)_2]$ and with di-*n*-butyl phenylboronate $[BPh(OBu^n)_2]$ and other esters of phenylboronic acid, have been investigated in order to compare these reactions with those of boric esters, and to compare the fluorine with the chlorine systems.

Boron trifluoride reacted readily with di-*n*-butyl *n*-butylboronate at 0°, to give *n*-butylboron difluoride [see (1)] or *n*-butyl *n*-butylfluoroboronite [see (2)] in good yield, depending on the proportion in which the reagents were mixed :

$$BBu^n{\cdot}(OBu^n)_2 + 2BF_3 \longrightarrow BBu^n{\cdot}F_2 + 2BF_2{\cdot}OBu^n \quad (1)$$

$$3BBu^n{\cdot}(OBu^n)_2 + BF_3 \longrightarrow 3BBu^nF{\cdot}OBu^n + B(OBu^n)_3 \quad (2)$$

Reaction in equimolecular proportion [see (3)] was demonstrated with di-*n*-butyl phenylboronate :

$$BPh(OBu^n)_2 + BF_3 \longrightarrow BPhF{\cdot}OBu^n + BF_2{\cdot}OBu^n \quad (3)$$

n-Butyl *n*-butylfluoroboronite was also obtained [see (4)] from *n*-butyl difluoroboronite and di-*n*-butyl *n*-butylboronate, and was less stable than the corresponding phenyl compound, disproportionating readily at 20° according to (5) :

$$2BBu^n{\cdot}(OBu^n)_2 + BF_2{\cdot}OBu^n \longrightarrow BBu^nF{\cdot}OBu^n + B(OBu^n)_3 \quad (4)$$

$$2BBu^nF{\cdot}OBu^n \longrightarrow BBu^nF_2 + BBu^n(OBu^n)_2 \quad (5)$$

Boron trichloride and di-*n*-butyl phenylboronate gave phenylboron dichloride [analogous to (1)]. The difficulty of separation from *n*-butyl dichloroboronite, due to the proximity of boiling points, was overcome either (i) by adding to the mixture a trace of ferric chloride, which causes decomposition of the dichloroboronite at low temperature [3] [see (6)], or (ii) by using diethyl or di-*sec.*-butyl phenylboronate as the starting compound.

$$3BCl_2{\cdot}OBu^n \xrightarrow{FeCl_3} 3Bu^nCl + B_2O_3 + BCl_3 \quad (6)$$

In the former case, ethyl dichloroboronite was more readily separated, but even here the use of ferric chloride was preferred, and in the latter the *sec.*-butyl dichloroboronite initially formed decomposed at room temperature to *sec.*-butyl chloride.[3,4]

By mixing boron trichloride with di-*n*-butyl *n*-butylboronate or phenylboronate in equimolecular proportions, *n*-butyl *n*-butylchloroboronite or *n*-butyl chlorophenylboronite

[1] Brindley, Gerrard, and Lappert, *J.*, 1955, 2956.
[2] Torssell, *Acta Chem. Scand.*, 1954, **8**, 1779.
[3] Gerrard and Lappert, *J.*, 1955, 3084.
[4] *Idem*, *J.*, 1951, 2545.

was obtained [analogous to (3)]. These boronites are quite stable. The butylchloroboronite was also obtained by a reaction analogous to (4), and also by the reaction (7).

$$BBu^n(OBu^n)_2 + BCl_2{\cdot}OBu^n \longrightarrow BBu^nCl{\cdot}OBu^n + BCl(OBu^n)_2 \quad . \quad . \quad . \quad . \quad (7)$$

The most convenient method for preparing *n*-butyl chlorophenylboronite was by mixing phenylboron dichloride with di-*n*-butyl phenylboronate [see (8)], as it was the only product of reaction.

$$BPh(OBu^n)_2 + BPhCl_2 \longrightarrow 2BPh{\cdot}Cl{\cdot}OBu^n \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

The preparations of *n*-butyl- and phenyl-boron dihalides, mentioned above, have advantages over earlier methods. First, the boronic esters are stable and easy to handle, and, secondly, mild reaction conditions are employed. Earlier methods [5–11] employed either the reaction between organometallic compounds and boron halides, or that between boron alkyls (or aryls, or aminodialkylborons) and boron or hydrogen halides. Methylboron difluoride was prepared from methylboronic anhydride and boron trifluoride.[12]

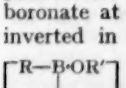
n-Butyl *n*-butyl- and phenyl-halogenoboronite are members of a new class of organoboron compound. They are unimolecular in *cyclo*hexane (owing to its instability the molecular weight of *n*-butyl *n*-butylfluoroboronite was not determined). They are of particular interest as they provide examples of tervalent boron compounds having three unlike groups attached to the boron atom. Their characterising physical constants are shown in the Table.

Compound	B. p./mm.	n_D^{20}	d_4^{20}
$BBu^nF{\cdot}OBu^n$	Volatile at 0·01 mm.	1·3900	0·888
$BBu^nCl{\cdot}OBu^n$	50°/1·5	1·4170	0·898
$BPhF{\cdot}OBu^n$	27°/0·005	1·4565	0·972
$BPhCl{\cdot}OBu^n$	65°/0·4 (m. p. −32°)	1·4996	1·021

Hydrogen chloride did not react, even after 7 hr. at 120°, with di-*n*-butyl *n*-butylboronate or with *n*-, *iso*-, or *sec*.-butyl phenylboronate, but with di-*tert*.-butyl phenylboronate it produced rapid dealkylation [see (9)] at 20°. Hydrogen bromide produced

$$BBu^n(OBu^t)_2 + 2HCl \longrightarrow BBu^n(OH)_2 + 2Bu^tCl \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

partial dealkylation of di-*n*-butyl phenylboronate and of (+)-di-2-methylheptyl phenylboronate at 120°. In the latter case the 2-bromo-octane obtained was preponderantly inverted in configuration. These results may be interpreted as involving an initial protonisation of one oxygen atom to afford a halide ion and a cation (inset). This either yields a carbonium cation if the alkyl group R′ is electron-releasing (*e.g.*, Bu^t), or reacts by an in-line attack of Hal^- on the carbon atom attached to the protonated oxygen if the alkyl group is of weaker electron-releasing type (*e.g.*, 2-methylheptyl).



In these reactions of boronates a broad similarity to those of borates may be discerned. Thus boron trifluoride reacts with tri-*n*-butyl borate to give *n*-butyl difluoroboronite,[13] although di-*n*-butyl fluoroboronate does not exist; hence reactions analogous to (2), (3), and (4) are not found in the boron trifluoride–borate systems. Boron trichloride does react with trialkyl borates to give alkoxyboron chlorides [3,4,14,15] [analogous to (1), (2), (3), and (8)]; and alkyl dichloroboronites also react with trialkyl borates [15] [analogous to (4)] to give dialkyl chloroboronates. The readier dealkylation of tri-*tert*.-butyl borate than of its *n*-, *iso*-, and *sec*.-isomers is also similar,[4] whilst the preponderant inversion of

[5] Krause and Nitzsche, *Ber.*, 1922, **55**, 1261; Krause, D.R.-P., 371,467/1924.
[6] Wiberg and Buchheit as quoted by Goubeau, F.I.A.T. Review of German Science (1939—46), Inorganic Chemistry, Vol. I, pp. 215—238.
[7] Michaelis *et al.*, *Ber.*, 1880, **13**, 58; 1882, **15**, 180; 1894, **27**, 244; *Annalen*, 1901, **315**, 19.
[8] Borisov, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*, 1951, 402.
[9] Burg and Banus, *J. Amer. Chem. Soc.*, 1954, **76**, 2537.
[10] Becher, *Z. anorg. Chem.*, 1953, **271**, 243.
[11] Booth and Kraus, *J. Amer. Chem. Soc.*, 1952, **74**, 1415.
[12] Burg, *ibid.*, 1940, **62**, 2228.
[13] Lappert, *J.*, 1955, 784.
[14] Wiberg and Smedsrud, *Z. anorg. Chem.*, 1935, **225**, 204.
[15] Lappert, *J.*, 1956, in the press.

the 2-bromo-octane obtained from (+)-tri-2-methylheptyl borate and hydrogen bromide [16] shows also the general resemblance of the two systems.

Experimental

Preparations and Techniques.—Boron trifluoride was prepared by Booth and Willson's method; [17] the trichloride was the commercial product purified by redistillation. Hydrogen chloride was prepared by action of concentrated sulphuric acid on anhydrous ammonium chloride and hydrogen bromide by Gerrard's method.[18] Both gases were dried by passage through a phosphoric oxide tower. The boronates were prepared by the method of Brindley, Gerrard, and Lappert.[1] Determination of boron in phenylboronates and derivatives was by hydrolysis to phenylboronic acid, which was estimated as a weak monobasic acid, after neutralisation, in the presence of mannitol. With *n*-butyl boronates and its derivatives a similar method was not practicable, owing to the weakness of *n*-butylboronic acid, and hence, following Snyder, Kuck, and Johnson,[19] the acid was oxidised and hydrolysed to boric acid by the addition of hydrogen peroxide (30%; 15 minutes' standing). Chlorine and fluorine were estimated (acidimetrically) as hydrogen halide formed on hydrolysis; some results were checked by the Volhard method (Cl) and for fluoride by gravimetric analysis (as CaF_2). The molecular weights were determined by freezing-point depressions in *cyclo*hexane under nitrogen.

Interaction of Boron Trifluoride with Boronates.—(a) *With di-*n*-butyl* n*-butylboronate.* Boron trifluoride was bubbled through the boronate (16·00 g., 1 mol.) at 0° until the solution was saturated, the increase in weight being 10·25 g. [Calc. for BF_3 (2 mols.): 10·30 g.]. n-*Butylboron difluoride* (6·70 g., 81%), a violently fuming liquid, was withdrawn at 20°/17 mm., condensed at −80°, and distilled; it had b. p. 34—36°/760 mm., n_D^{19} 1·3300 (Found: F, 33·8; B, 9·7. $C_4H_9BF_2$ requires F, 35·8; B, 10·2%). The non-volatile residue afforded on distillation *n*-butyl difluoroboronite (16·10 g., 85%), b. p. 50—53°/23 mm., n_D^{23} 1·3840 (Found: C, 39·8; H, 7·7. Calc. for $C_4H_9OBF_2$: C, 39·4; H, 7·5%), and a residue (1·82 g.). The yields are based on scheme (1).

The gas was passed into the boronate (24·68 g., 3 mols.) at 0° until 1 mol. of the gas (2·62 g.) was absorbed. The mixture was set aside for 2 hr. at 20° and then volatile matter was removed, with shaking, and after 6 hr. n-*butyl* n-*butylfluoroboronite* (16·21 g., 88%), n_D^{20} 1·3892 (Found: F, 11·3; B, 6·4. $C_8H_{18}OBF$ requires F, 11·8; B, 6·8%), had collected in a trap at −80°. The residue afforded on distillation a fore-run (2·13 g.), b. p. 26—69°/0·2 mm., n_D^{20} 1·4078, and tri-*n*-butyl borate (8·70 g., 98%), b. p. 70°/0·2 mm., n_D^{20} 1·4116 (Found: B, 4·7. Calc. for $C_{12}H_{27}O_3B$: B, 4·7%). Yields are based on scheme (2).

(b) *With di-*n*-butyl phenylboronate.* The gas was passed into the boronate (22·2 g., 1 mol.) at 0° until 1 mol. (6·8 g.) had been absorbed (about 2 hr.). On evacuation (25°/0·05 mm.) a condensate was collected at −70°. The residue afforded *n*-butyl fluorophenylboronite (12·3 g., 72%) on distillation, b. p. 40—42°/0·04 mm., n_D^{20} 1·4532 (Found: F, 9·2; B, 5·9%), and a residue (1·0 g.). The impure ester had b. p. 27°/0·005 mm., n_D^{20} 1·4605 (Found: C, 65·2; H, 8·3; F, 10·2; B, 5·7%; *M*, 198. Calc. for $C_{16}H_{14}OBF$: C, 66·7; H, 7·8; F, 10·6; B, 6·0%; *M*, 180), on redistillation, and was a fuming liquid. The combined condensates (10·55 g. Calc. for $BF_3{\cdot}OBu^n$: 11·6 g.) consisted of crude *n*-butyl difluoroboronite, b. p. 46°/15 mm., n_D^{20} 1·3900. The yields are based on scheme (3).

Interaction of n-*Butyl Difluoroboronite with Di-*n*-butyl* n-*Butylboronate.*—The difluoroboronite [18] (4·42 g., 1 mol.) and the boronate (15·52 g., 2 mols.) were mixed at 23°. The reaction was endothermic, a temperature drop of 7° being noted. The mixture was kept at 0·01 mm. whilst shaken for 6 hr. A condensate of *n*-butyl *n*-butylfluoroboronite (10·8 g., 93%), n_D^{20} 1·3922, d_4^{20} 0·888 (Found: F, 11·6; B, 6·3%), was collected in a trap at −80°, and the major product isolated from the non-volatile residue was tri-*n*-butyl borate (8·10 g., 97%), b. p. 117°/16 mm., n_D^{20} 1·4110 (Found: B, 4·7%). The yields are based on scheme (4).

Disproportionation of n-*Butyl* n-*Butylfluoroboronite at 25°.*—The freshly prepared boronite (6·60 g.) was kept in a desiccator at 25° for 5 days. At 20 mm., a condensate of *n*-butylboron difluoride (0·88 g., 39·2%), b. p. 35°/760 mm., n_D^{20} 1·3285 (Found: F, 35·1; B, 10·0%), was collected. The remainder, at 0·005 mm., afforded unchanged *n*-butyl *n*-butylfluoroboronite

[16] Gerrard and Lappert, *J.*, 1951, 1020.
[17] Booth and Willson, *Inorg. Synth.*, 1939, **1**, 21.
[18] Gerrard, *Research*, 1954, **7**, S20.
[19] Snyder, Kuck, and Johnson, *J. Amer. Chem. Soc.*, 1938, **60**, 105.

(3·90 g.; 59%), n_D^{20} 1·3896 (Found: F, 11·3; B, 6·5%), as a further condensate, whilst the non-volatile residue was di-*n*-butyl *n*-butylboronate (1·64 g., 37·2%), b. p. 113—115°/14 mm., n_D^{20} 1·4175 (Found: B, 5·03. Calc. for $C_{12}H_{27}O_2B$: B, 5·1%). The yields are based on scheme (5).

Interaction of Boron Trichloride with Boronates.—(a) *With di-*n*-butyl* n*-butylboronate.* The boronate (15·3 g., 1 mol.) was added (1·6 hr.) dropwise with shaking to boron trichloride (8·4 g., 1 mol.) at −70°. On evacuation (20°/1 mm.) crude *n*-butyl dichloroboronite (9·7 g., 93%) was collected as a condensate at −80°, which was purified by four distillations (Found: Cl, 46·2; B, 6·4. Calc. for $C_4H_9OCl_2B$: Cl, 45·8; B, 7·0%). The non-volatile residue afforded n-*butyl* n-*butylchloroboronite* (8·1 g., 64%), b. p. 48—52°/2 mm., n_D^{23} 1·4170, d_4^{20} 0·898 (Found: C, 54·5; H, 8·7; Cl, 21·0; B, 6·1%; *M*, 175. $C_8H_{18}OClB$ requires C, 54·5; H, 10·2; Cl, 20·1; B, 6·1%; *M*, 177), as a fuming, colourless liquid. Yields are based on: $BBu^n(OBu^n)_2 \xrightarrow{+BCl_3} BBu^nCl{\cdot}OBu^n + BCl_2{\cdot}OBu^n$.

(b) *With phenylboronates* (2 : 1). Preliminary experiments showed that mixing boron trichloride (2 mols., or more) with either the ethyl or the *n*-butyl ester (1 mol.) of phenylboronic acid led to difficulty in separation of pure phenylboron dichloride, the chlorine content of the product being invariably low; hence we report below only those experiments, with these two esters, wherein ferric chloride was added to the mixture.

Di-*n*-butyl phenylboronate (20·5 g., 1 mol.) was added to boron trichloride (20·5 g., 2 mols.) and ferric chloride (0·21 g.) at −80°. The mixture was kept at 20° for 20 min., whereupon volatile matter was removed at 20 mm. A solid cake remained, which was extracted with methylene dichloride (3 × 25 c.c.). The residue, after removal of solvent from this extract, was crude phenylboron dichloride (10·8 g., 81%), b. p. 62°/18 mm., n_D^{18} 1·4392, d_4^{20} 1·194 (Found: Cl, 44·0; B, 6·8. Calc. for $C_6H_5Cl_2B$: Cl, 44·6; B, 6·8%).

Diethyl phenylboronate (6·0 g., 1 mol.) with boron trichloride (7·9 g., 2 mols.) and ferric chloride (0·01 g.) similarly (violent reaction) afforded the dichloride (4·6 g., 80%), b. p. 57°/8 mm., n_D^{20} 1·4385 (Found: Cl, 44·3; B, 6·9%).

By the same technique, but in absence of ferric chloride, di-*sec.*-butyl phenylboronate (20·2 g., 1 mol.) and boron trichloride (20·2 g., 2 mols.) afforded the dichloride (10·4 g., 76%), b. p. 62°/18 mm., n_D^{20} 1·4387 (Found: Cl, 43·7; B, 6·8%). In these experiments yields are based on: $BPh(OR)_2 + 2BCl_3 \longrightarrow BPhCl_2 + 2BCl_2{\cdot}OR$ (decomp.).

(c) *With di-*n*-butyl phenylboronate* (1 : 1). To the trichloride (12·5 g., 1 mol.) at −70°, the boronate (25·0 g., 1 mol.) was added (1 hr.) with shaking. The mixture set solid, but melted at 15°. A condensate (16·6 g.) was collected in a trap at −80°, when the mixture was shaken for 4 hr. at 40°/10 mm. and 15 hr. at 20°/0·4 mm.; this was largely *n*-butyl dichloroboronite, contaminated with *n*-butyl chloride. The dichloroboronite (12·3 g., 70%) was isolated from this condensate by distillation (b. p. 28°/11 mm.) (Found: Cl, 45·3; B, 7·1%). The non-volatile residue afforded n-*butyl chlorophenylboronite* (10·0 g., 48%), b. p. 70—71°/0·5 mm., n_D^{20} 1·4760 (Found: Cl, 18·1; B, 5·5%; *M*, 191. $C_{10}H_{14}OClB$ requires Cl, 18·1; B, 5·5%; *M*, 196), as a fuming, colourless liquid; and a white, solid residue (10·7 g.), on extraction with dry *n*-pentane, was identified as phenylboron oxide, m. p. 212—213° (Found: B, 10·0. Calc. for C_6H_5OB: B, 10·4%). The yields are based on: $BPh(OBu^n)_2 + BCl_3 \longrightarrow BPhCl{\cdot}OBu^n + BCl_2{\cdot}OBu^n$.

Interaction of n-*Butyl Dichloroboronite with Di-*n*-butyl* n-*Butylboronate.*—To the dichloroboronite [4] (11·4 g., 1 mol.) at −70°, the boronate (15·7 g., 1 mol.) was added during ½ hr. with shaking. After 13 hr. at 20° and passage of dry nitrogen through the mixture, two distillations afforded *n*-butyl *n*-butylchloroboronite (10·0 g., 77%), b. p. 36—40°/1 mm., n_D^{20} 1·4152 (Found: Cl, 20·3; B, 5·9%). Other fractions were difficult to purify. The yield is based on scheme (7).

To the purified dichloroboronite (11·7 g., 1 mol.) at −70° was added (0·3 hr.) dropwise with shaking the boronate (31·8 g., 2 mols.). The mixture was set aside for 3 days at −70° whereupon it partially crystallised. Distillation afforded pure *n*-butyl *n*-butylchloroboronite (20·1 g., 76%), b. p. 66—70°/10 mm., n_D^{20} 1·4157 (Found: Cl, 20·5; B, 6·4%). The higher-boiling fraction, from which it was difficult to remove traces of the chloro-ester, was tri-*n*-butyl borate, b. p. 104°/12 mm., n_D^{20} 1·4110 (Found: B, 4·6%). The yield is based on: $2BBu^n(OBu^n)_2 + BCl_2{\cdot}OBu^n \longrightarrow 2BBu^nCl{\cdot}OBu^n + B(OBu^n)_3$.

*Interaction of Phenylboron Dichloride and Di-*n*-butyl Phenylboronate.*—The dichloride (1·62 g., 1 mol.) and the boronate (2·38 g., 1 mol.) were mixed at 10°. There was some heat of reaction. Distillation afforded *n*-butyl chlorophenylboronite (3·86 g., 97%), b. p. 58°/0·2 mm., n_D^{19} 1·4980, d_4^{20} 1·021 (Found: Cl, 17·7; B, 5·5%), and a solid residue (0·15 g.).

Interaction of Hydrogen Chloride and Boronates.—(a) *With di-*n*-, -iso-, and -sec.-butyl phenylboronate and di-*n*-butyl* n*-butylboronate, severally.* In none of these cases was reaction observed.

The dry gas was bubbled through the ester (about 5 g.), both at 15° (30 hr.) and at 120° (7 hr.). After evacuation (20 mm.) no change in weight was observed [except in the case of $BPh(OBu^s)_2$] and distillation gave a high yield of unchanged ester, characterised by b. p., n_D^{20}, and analysis for boron. In the di-*sec.*-butyl phenylboronate experiment the amount of boronate recovered was only 65%, there being a high-boiling residue.

(b) *With di-*tert.*-butyl phenylboronate.* The gas was bubbled through a vessel containing the ester (1·95 g.) at 20°, connected to a trap at −80°. Within 5 min., a precipitate formed and the mixture set solid. Xylene (5 c.c.) was added and the gas was passed through the mixture for a further 30 min. A condensate of *tert.*-butyl chloride (1·26 g., 82%) saturated with hydrogen chloride was collected in the trap. After addition of lead carbonate (to remove hydrogen chloride), this condensate was distilled; it had b. p. 50—51°/760 mm., n_D^{17} 1·3873 (Found: Cl, 37·8. Calc. for C_4H_9Cl: Cl, 38·4%). Xylene was removed from the residue at 0·001 mm., and phenylboronic acid (1·05 g. Calc.: 1·02 g.) (Found: B, 9·6. Calc. for $C_6H_7O_2B$: B, 9·1%) remained as a white solid. Yields are based on scheme (9).

Interaction of Hydrogen Bromide and Boronates.—(a) *With di-*n*-butyl phenylboronate.* The dry gas was bubbled through the boronate (5·1 g.) at 20° for 14 hr. Distillation afforded the unchanged ester (4·0 g., 79%), b. p. 84°/0·4 mm. (Found: B, 4·6%), and a solid residue (0·55 g.). A condensate (0·45 g., 7·8%) was crude *n*-butyl bromide, b. p. 84—86°, n_D^{20} 1·4300.

When the gas was passed through the ester (2·80 g.) at 120° for 7 hr., the mixture set solid. At 20°/0·05 mm., *n*-butyl bromide (1·90 g., 58%) was collected at −70°. After being washed and dried ($MgSO_4$), this had b. p. 97°/760 mm., n_D^{21} 1·4352. The non-volatile residue afforded unchanged boronate (0·80 g., 28·6%), b. p. 60—68°/0·3 mm. The residue (1·08 g., 74%) was phenylboronic acid, m. p. 213—216° (from water), which was converted into the anhydride (Found: B, 10·2%).

(b) *With (+)-*2*-methylheptyl phenylboronate.* The gas was passed through the ester (2·24 g., α_D^{20} +15·08°, from ROH having α_D^{20} +7·53°; in each case $l = 1$) for 7 hr. at 120°. On cooling, the mixture set solid. Excess of gas was removed by suction at 20 mm. The increase in weight was 1·04 g. (Calc.: 1·047 g. for complete reaction). Distillation afforded (−)-2-bromo-octane (1·60 g., 67%), b. p. 74°/10 mm., n_D^{20} 1·4504, α_D^{20} −28·4° ($l = 1$), and a residue of crude phenylboronic acid (0·89 g.), m. p. 212—216° (from water). Yields in these experiments are based on: $BPh(OR)_2 + 2HBr \longrightarrow 2RBr + BPh(OH)_2$.

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177. *The Mucilages of* Hibiscus esculentus (*Okra or Bamia fellahi*) *and* Corchorus olitorius (*Mulukhia*).

By El S. Amin.

The purification and monosaccharide degradation products of these two mucilages are reported.

Okra (Family Malvaceæ, Order Malvales) is widely cultivated and the pods are used as common food in Egypt. In water the minced pods yield a mucilage indistinguishable in appearance from solutions of other plant gums and mucilages. Partial hydrolysis of the mucilage gave three galactobioses, one of which has been proved to be 4-*O*-D-galacto-pyranosyl-D-galactose.[1] The following oligosaccharides were found[2] as hydrolytic fragments, suggesting that the linkages involved are present in the polysaccharide: 2-*O*-(D-galactopyranosyluronic acid)-L-rhamnose, galactosyl → (galactosyluronic acid) → rhamnose, and (galactosyluronic acid) → rhamnosyl → galactose.

In our work, the mucilage was extracted with water at room temperature and purified by reprecipitation from alcohol, formation of a water-insoluble copper complex, and dialysis. Attempts to separate the pentoses and uronic acid by fractional precipitation were unsuccessful. The substance had a low positive optical rotation and a slight reducing action on Fehling's solution. Hydrolysis of the pure mucilage by mineral acid and paper

[1] Whistler and Conrad, *J. Amer. Chem. Soc.*, 1954, **76**, 1673.
[2] *Idem, ibid.*, p. 3544.

chromatography gave galactose (80%), rhamnose (10%), and a little arabinose (3%) and galacturonic acid (6%). The mucilage was then acetylated, deacetylated, and methylated with methyl sulphate and sodium hydroxide followed by methyl iodide and silver oxide. Fractionation and hydrolysis of the main fraction yielded 2 : 3 : 4 : 6-tetra- (12%), 2 : 3 : 6-tri- (60%), and 2 : 6-di-*O*-methylgalactose (6%), 3 : 4-di-*O*-methylrhamnose (8%), and (?)-*O*-methyl-L-rhamnose but no arabinose derivative. This suggests that the main linkage among the hexose units is 1 : 4, and that rhamnose is linked through $C_{(1)}$ and $C_{(2)}$ and is in the pyranose form. The dimethylgalactose may result from incomplete methylation or from demethylation of the methylated sugar during methanolysis.

Corchorus (Family Tiliaceæ, Order Malvales) is also widely cultivated and the leaves are a popular food in Egypt. When the leaves are minced in water, a mucilage is dispersed, the viscosity of which is greatly diminished by boiling. The mucilage was prepared by extraction with water at room temperature, and purified in the same way as the okra mucilage. It gave a white amorphous substance difficultly soluble in water, with a low specific rotation and slight reducing action on Fehling's reagent. Pentoses could not be separated by fractional precipitation. Hydrolysis of the mucilage by mineral acid and paper chromatography gave galactose (60%), rhamnose (20%), arabinose (12%), xylose (6%), and uronic acid (1·2%). Methylation as above and fractionation gave a main fraction with a low specific rotation. Hydrolysis yielded 2 : 3 : 4 : 6-tetra- (3·5%), 2 : 3 : 6-tri- (58%), and 2 : 6-di-*O*-methylgalactose (8%), 3 : 4-di-*O*-methylrhamnose (14%), and (?)-*O*-methylrhamnose (10%). Xylose and arabinose derivatives were absent. The above derivatives prove that the hexose units are mainly linked through $C_{(1)}$ and $C_{(4)}$, and rhamnose through $C_{(1)}$ and $C_{(2)}$, being present in the pyranose form.

Experimental

Chromatography was carried out on Whatman No. 1 filter-paper sheets by the descending method [3] at room temperature, with butan-1-ol–ethanol–water (5 : 1 : 4 v/v). Sugars and methyl-sugars were detected with *p*-anisidine hydrochloride as spray reagent. Evaporations were done under reduced pressure at 50° unless otherwise stated. Specific rotations and viscosities were measured at 20°. Treatments with alkali were under nitrogen. The results were calculated on an ash-free basis.

Preparation of Okra Mucilage.—Okra pods (5 kg.), harvested in August, 1953, at Alexandria, Egypt, were cut into thin slices and minced in 0·1N-hydrochloric acid (9 l.) for 24 hr. The mucilage which was dispersed in the aqueous solution was squeezed through a sieve (mesh 2 mm.). Re-extraction was carried out and the residue discarded. The aqueous extract was shaken with charcoal for 4 hr. at room temperature, then twice centrifuged (3500, then 24,000 r.p.m.). The clear liquor was poured into 96% ethyl alcohol (5 parts) with stirring, giving a white fibrous material. To reduce the ash content (2%) the product was redispersed in water, 5% hydrochloric acid was added to a final normality of 1, and the mucilage dialysed for 24 hr. (yield 210 g., 2%). Further purification was effected by dissolution in N-sodium hydroxide, acidification with acetic acid, centrifugation, and precipitation with alcohol (yield 200 g., 4%). The yield of the mucilage was not quantitative as much of it remained in the unruptured cells. The product was dissolved in ammonia (*ca.* 2N), and a neutral solution was treated with 25% aqueous copper chloride. The resultant insoluble copper complex was removed on the centrifuge and washed with water and alcohol, followed by ethanolic hydrogen chloride (5%) until the washings were copper-free, and finally with ethanol until chloride-free. The product was dried to constant weight (160 g.) in a vacuum at 50°. The mother-liquor from the copper complex was concentrated to 200 c.c. and treated with alcohol (5 parts). The precipitate was treated as above, giving an amorphous white polysaccharide (4·5 g.).

Properties of Okra Mucilage.—It was a white amorphous substance insoluble in organic solvents, and dissolved with difficulty in water, but easily in alkali, giving a viscous solution. It had little reducing action on Fehling's reagent, and was unaffected by saliva during 10 min. (Found : sulphated ash, 0·1; N, 0·08%); it had $[\alpha]_D$ +26° (*c* 0·8 in N-NaOH), $\eta_{sp.}$ 0·22 (*c* 0·1 in N-NaOH), and gave 6% of uronic acid by Lefèvre and Tollens's method.[4] According to a report from Prof. Dr. M. S. Ridi, Kasr El Aini, Faculty of Medicine, Cairo, the composition of Okra pods was : water 85·7, carbohydrate 6·3, protein 3·0, ash 1·3, fat 0·2%, Cross cal./100 g. 40·0.

[3] Partridge, *Biochem. J.*, 1948, **42**, 238.
[4] Lefèvre and Tollens, *Ber.*, 1907, **40**, 4513.

Acid Hydrolysis of Okra Mucilage.—A portion (420 mg.) was heated with N-sulphuric acid (30 c.c.) at 100° in a sealed tube for 12 hr. The mixture in which was suspended a small amount of flocculent material (10 mg.) was filtered and the filtrate neutralised with 0·01N-barium hydroxide, barium sulphate removed, and the solution evaporated to dryness. The residue was extracted with boiling methanol until the extracts were non-reducing, leaving a residue of barium salts (*A*) (30 mg.). The methanol extracts were de-ionised with a mixture of Amberlite resins IR-120 and IRA-400 and concentrated to a syrup (*B*) (280 mg.). Examination of a portion on the paper chromatogram gave spots corresponding to galactose (R_G 0·07), rhamnose (R_G 0·30), and arabinose (R_G 0·12). Quantitative determination of the sugars[5] indicated galactose 80, arabinose 3, and rhamnose 10%.

The syrup *B* (120 mg.) was separated on the paper chromatogram, and appropriate fractions were extracted with hot methanol. The first fraction had $[\alpha]_D$ +78° (*c* 0·9 in N-H_2SO_4) and gave D-galactose methylphenylhydrazone[6] (60 mg.), m. p. and mixed m. p. 185° (decomp.), and mucic acid,[7] m. p. and mixed m. p. 215°. The second fraction, $[\alpha]_D$ +9° (equil.; *c* 1·0), was treated with alcoholic benzoylhydrazine,[8] giving crystalline L-rhamnose benzoylhydrazone (8 mg.), m. p. and mixed m. p. 183° (decomp.). The third fraction, $[\alpha]_D$ +104° (equil.; *c* 0·3 in H_2O), gave L-arabinose α-benzoylphenylhydrazone[6] (3 mg.), m. p. and mixed m. p. 170°.

Examination of the barium salt (A). A portion (30 mg.) was treated with dilute hydrochloric acid, then chloride ion was removed by silver carbonate. After filtration, hydrogen sulphide was passed into the filtrate, the insoluble silver sulphide removed, and the filtrate concentrated to a syrup (4 mg.). This was examined on the paper chromatogram alongside galacturonic acid. There was one spot corresponding to galacturonic acid. The syrup gave a brick-red precipitate when warmed with basic lead acetate, indicating the presence of galacturonic acid, a test not given by glucuronic acid or mannuronic acid.[8]

Acetylation of Okra Mucilage.—The dry powdered polysaccharide (5 g.) was warmed with pyridine (100 c.c.) for 2 hr. at 70°, then cooled and kept overnight at room temperature. Acetic anhydride (40 c.c.) was added dropwise during ½ hr. The mixture was then incubated at 52° for 3 days. The clear solution was diluted with acetic acid (100 c.c.) and poured in stirred ethyl alcohol (2 l.). The white amorphous material was centrifuged, washed with alcohol and ether, and dried (yield, 4 g.). Reacetylation was carried out in the same way, giving a product (3·2 g.) having $[\alpha]_D$ +40° (*c* 0·8 in $CHCl_3$).

Methylation of Okra Mucilage.—(*a*) A portion (6·5 g.) was suspended in water (40 c.c.) and allowed to swell for 2 hr. The air was displaced by nitrogen, and the flask was cooled to 5°. Sodium hydroxide solution (30%; 80 c.c.) was added with vigorous stirring. After 2 hr., dimethyl sulphate (40 c.c.) was added during 8 hr. Stirring was continued overnight, and the reaction was completed at 50° for an hour. The mixture was cooled and treated with 30% sodium hydroxide solution (100 c.c.), followed by methyl sulphate (50 c.c.) as before. It was then neutralised with 0·5N-sulphuric acid and dialysed for 24 hr. The methylation was repeated six times in presence of acetone (80 c.c. each time) at room temperature. The final product was extracted with chloroform, and the chloroform extract twice methylated as above, then twice treated with methyl iodide (80 c.c.) and silver oxide (40 g.) for 12 hr., giving a product (4·2 g.), $[\alpha]_D$ +52° (*c* 0·8 in $CHCl_3$) (Found: OMe, 37·5%).

(*b*) A portion (3 g.) of the acetylated mucilage was dispersed in acetone (150 c.c.) and exhaustively methylated as above {yield 2·4 g.; $[\alpha]_D$ +60° (*c* 1 in $CHCl_3$) (Found: OMe, 39%)}.

The methylated product was fractionated by successive extractions under reflux with mixtures (50 c.c.) of light petroleum (b. p. 60—80°) and chloroform in the following proportions: 19 : 1; 10 : 1; 17 : 3; 4 : 1. The product dissolved almost completely in the last mixture, and the fraction obtained was unchanged in methoxyl content.

Hydrolysis of Methylated Okra Mucilage.—A portion (0·6 g.) was heated for 12 hr. at 100° with 3% methanolic hydrogen chloride, then neutralised with cold ethereal diazomethane, concentrated at room temperature, and refluxed with 4% hydrochloric acid for 7 hr. The solution was neutralised with silver carbonate, de-ionised with a mixture of Amberlite resins IR-120 and IRA-400, and evaporated to a syrup (540 mg.). Examination on the paper chromatogram indicated the presence of 2 : 3 : 4 : 6-tetra-*O*-methylgalactose, 3 : 4-di-*O*-methylrhamnose (R_G 0·86), 2 : 3 : 6-tri- (R_G 0·71) and 2 : 6-di-*O*-methylgalactose (R_G 0·41), and (?)-*O*-methylrhamnose (R_G 0·57). Quantitative determination by the alkaline hypoiodite

[5] Flood, Hirst, and Jones, *J.*, 1948, 1679; Nicolet and Shinn, *J. Amer. Chem. Soc.*, 1941, **63**, 1456.
[6] Hirst, Jones, and Woods, *J.*, 1947, 1048.
[7] Heyne and Whistler, *J. Amer. Chem. Soc.*, 1948, **70**, 2249.
[8] Stacey, *J.*, 1939, 1529.

procedure [9] gave 2 : 3 : 4 : 6-tetra-*O*-methylgalactose and 3 : 4-di-*O*-methylrhamnose (20%), 2 : 3 : 6-tri- (60%) and 2 : 6-di-*O*-methylgalactose (6%), and (?)-*O*-methylrhamnose (9%).

Another portion (200 mg.) of the hydrolysate was separated on the paper chromatogram, and fractions were extracted with methanol. The first fraction (Found : OMe, 44·3. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5; for $C_8H_{16}O_5$: OMe, 32·3%) appeared to contain 2 : 3 : 4 : 6-tetra-*O*-methylgalactose (12%) and 3 : 4-di-*O*-methylrhamnose (8%). That fraction was heated with methanolic 2% hydrogen chloride under reflux for 7 hr.; fractional distillation in a vacuum then gave: fraction (*a*), b. p. 120—125°/0·001 mm., hydrolysed by N-sulphuric acid for 6 hr. to a syrup, which gave 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-galactosylamine (6 mg.), m. p. and mixed m. p. 194°; and fraction (*b*), b. p. 130—140°/0·001 mm., hydrolysed as above to a syrup, which was oxidised with bromine water to 3 : 4-di-*O*-methyl-L-rhamnolactone (3 mg.), m. p. and mixed m. p. 78°, $[\alpha]_D$ −114° (equil.; *c* 0·2 in H_2O). The second fraction had $[\alpha]_D$ +87° (*c*, 0·9) (Found : OMe, 38·5. Calc. for $C_9H_{18}O_6$: OMe, 41·8%) and was oxidized with bromine [10] to 2 : 3 : 6-tri-*O*-methyl-D-galactonolactone (from ether–light petroleum) (6 mg.), m. p. and mixed m. p. 99°, $[\alpha]_D$ −40·5° (*c* 0·8 in H_2O).

Corchorus *Mucilage*.—The leaves (5 kg.) were freshly harvested in August, 1953, at Alexandria, Egypt. They were cut and minced in 0·1N-hydrochloric acid (9 l.) for 24 hr. The mucilage was then isolated as for Okra mucilage (yield 100 g., 2%). The yield of polysaccharide from the soluble copper complex was 0·5 g. The yield of mucilage was not quantitative as some still remained in the unruptured cells.

Properties of Corchorus *Mucilage*.—These were similar to those of Okra mucilage (Found : sulphated ash, 0·1; N, 0·03%); the material had $[\alpha]_D$ +39° (*c* 0·6 in N-NaOH), $\eta_{sp.}$ 0·1 (*c* 0·1 in N-NaOH), and gave 3% of uronic acid.

Hydrolysis of Corchorus *Mucilage*.—A portion (500 mg.) was heated with N-sulphuric acid (35 c.c.) at 100° for 24 hr. in a sealed tube. Flocculent material (8 mg.) was filtered off and the filtrate neutralised with barium carbonate. It was de-ionised as above and concentrated to a syrup (320 mg.), which on the paper chromatogram gave spots corresponding to galactose (R_G 0·07), rhamnose (R_G 0·30), arabinose (R_G 0·12), and xylose (R_G 0·15). Quantitative determination [5] of the sugars indicated galactose (60%), rhamnose (20%), arabinose (12%), and xylose (6%).

A portion (150 mg.) of the hydrolysate was separated on the paper chromatogram and the fractions were extracted with hot methanol. The first fraction had $[\alpha]_D$ +78° (*c*, 0·9 in N-H_2SO_4) and gave D-galactose methylphenylhydrazone (40 mg.), m. p. and mixed m. p. 185°, and mucic acid, m. p. and mixed m. p. 215°. The second fraction had $[\alpha]_D$ +9·4° (equil.; *c* 0·3) and gave L-rhamnose benzoylhydrazone (15 mg.), m. p. and mixed m. p. 183° (decomp.). The third fraction had $[\alpha]_D$ +106° (equil.; *c* 0·2 in H_2O) and gave L-arabinose α-benzoylphenylhydrazone (5 mg.), m. p. and mixed m. p. 170°. The fourth fraction gave di-*O*-benzylidene-D-xylose dimethyl acetal [11] (3 mg.), m. p. and mixed m. p. 211°.

Acetylation of Corchorus *Mucilage*.—A portion (5·5 g.) was twice acetylated in the same way as Okra mucilage (yield 3 g.). It had $[\alpha]_D$ +46° (*c* 0·9 in $CHCl_3$).

Methylation of Corchorus *Mucilage*.—(*a*) A portion (7 g.) was exhaustively methylated with methyl sulphate and sodium hydroxide, then esterified by two treatments with methyl iodide and silver oxide (yield 4·3 g.). The product had $[\alpha]_D$ +58° (*c* 0·6 in $CHCl_3$) (Found : OMe, 36%). The methylated product was fractionated by successive extractions with light petroleum–chloroform as before. The main fraction was soluble in the 4 : 1 mixture and had the same methoxyl content as the other fractions and $[\alpha]_D$ +51° (*c* 0·7 in $CHCl_3$).

Hydrolysis of Methylated Corchorus *Mucilage*.—A portion (560 mg.) was heated for 12 hr. at 100° with methanolic hydrogen chloride, then neutralised with cold ethereal diazomethane, concentrated, and refluxed with 4% hydrochloric acid for 7 hr. The solution was neutralised with silver carbonate, de-ionised as usual, and evaporated to a syrup (yield 490 mg.). Examination on the paper chromatogram indicated presence of 2 : 3 : 4 : 6-tetra-*O*-methylgalactose, 3 : 4-di-*O*-methylrhamnose (R_G 0·86), 2 : 3 : 6-tri- (R_G 0·71) and 2 : 6-di-*O*-methylgalactose (R_G 0·41), and (?)-*O*-methylrhamnose (R_G 0·57). Quantitative determination [9] gave 2 : 3 : 4 : 6-tetra-*O*-methylgalactose and 3 : 4-di-*O*-methylrhamnose (17·5%), 2 : 3 : 6-tri- (58%) and 2 : 4-di-*O*-methylgalactose (6%), and (?)-*O*-methylrhamnose (10%). Another portion of the hydrolysate (180 mg.) was chromatographed, the methylated sugars were located, and sections of the different fractions extracted with hot methanol. The first fraction (Found : OMe, 36·3.

[9] Hirst, Hough, and Jones, *J.*, 1949, 928.
[10] Hough and Jones, *J.*, 1950, 1199.
[11] Breddy and Jones, *J.*, 1945, 738.

Calc. for $C_{16}H_{28}O_6$: OMe, 52·5; for $C_9H_{16}O_5$: OMe, 32·3%) contained 2 : 3 : 4 : 6-tetra-*O*-methylgalactose (3·5%) and 3 : 4-di-*O*-methylrhamnose (14%). This fraction was heated with methanolic 2% hydrogen chloride under reflux for 7 hr. The methylated sugars were fractionally distilled in a vacuum, giving fractions: (*a*) b. p. 120—125°/0·001 mm., hydrolysed by N-sulphuric acid (6 hr.) to a syrup (Found: OMe, 49·2%), and yielding 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-galactosylamine (4 mg.), m. p. and mixed m. p. 194°; and (*b*) b. p. 130—140°/0·001 mm., hydrolysed as above to a syrup, which was oxidised with bromine to 3 : 4-di-*O*-methyl-L-rhamnolactone, m. p. and mixed m. p. 78° $[\alpha]_D$ −116° (equil; *c* 0·3 in H_2O).

The second fraction had $[\alpha]_D$ +87° (*c* 0·9) (Found: OMe, 39·2. Calc. for $C_9H_{18}O_6$: OMe, 41·8%). It was oxidised with bromine [10] to 2 : 3 : 6-tri-*O*-methyl-D-galactonolactone (10 mg.), m. p. and mixed m. p. 99°, $[\alpha]_D$ −40° (*c* 1 in H_2O).

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178. *Chemical Action of Ionizing Radiations in Solution. Part XV.* Effect of Molecular Oxygen in the Irradiation of Aqueous Benzene Solutions with X-Rays.*

By M. DANIELS, G. SCHOLES, and J. WEISS.

The chemical effects of *X*-rays (200 kv) on aqueous benzene have been investigated further with particular reference to the nature of the products (in addition to phenol) formed in the presence of dissolved molecular oxygen. Under these conditions, small amounts of an aldehyde, probably mucondialdehyde, are produced; it is suggested that this is produced *via* the intermediary formation of organic peroxy-radicals.

THE chemical effects of *X*-rays on aqueous benzene were first investigated by Stein and Weiss,[1] who showed that phenol and diphenyl were the major products formed in the absence of oxygen. Using mixed neutron–γ-ray radiation from radioberyllium and also α-radiation from radon, they found [2] that, *in vacuo*, in addition to the above products obtained by irradiation with *X*-rays, there were formed polyphenols (quinol and catechol) and, in particular, an aldehyde, possibly of a mixture of mucondialdehyde and its partly or fully hydrogenated derivatives. It was thus supposed, in the first instance, that the formation of these additional products by densely ionizing radiations was possibly the result of multiple interactions caused by the high local concentration of radicals. In a later publication the same authors,[3] using a source giving predominantly γ-radiation, reported that oxygen enhanced the yield of aldehyde. Thus it seemed possible that ring fission was connected with the presence of oxygen in solution rather than with high radical concentrations, as it is well known [4] that oxygen is formed in aqueous systems irradiated with more densely ionizing radiations [neutrons (recoil protons), α-rays, etc.]. In view of these observations, we have investigated further the effects of 200-kv *X*-rays on aqueous benzene solutions containing oxygen, particularly with respect to more complex chemical changes in the benzene nucleus.

For these experiments, neutral aqueous benzene solutions were saturated with oxygen and irradiated with doses of the order of 8×10^{-4} ev/N per ml.

Lack of turbidity on irradiation was taken as an indication of the absence of any significant amounts of diphenyl. Indeed, only traces of this substance were detectable in concentrated ether extracts of the irradiated solutions.

A yellow colour formed on addition of alkali to the irradiated solution was discharged

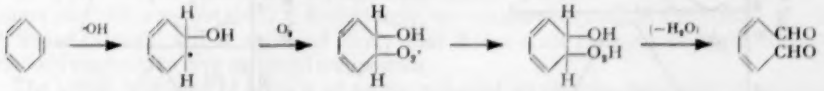
* Part XIV, *J.*, 1955, 2594.

[1] Stein and Weiss, *J.*, 1949, 3245.
[2] *Idem, ibid.*, p. 3254.
[3] *Idem, ibid.*, 1951, 3265.
[4] Bonet-Maury, *Compt. rend.*, 1948, **226**, 1363, 1445.

by acid. A faint "acid-Folin" reaction for polyphenols [3] was exhibited, and traces of catechol and quinol were detected by paper chromatographic analysis (Riley's method [5]). On reduction of the irradiated solution with sulphur dioxide before analysis, a slight increase in the amounts of detectable quinol was observed and this presumably indicated the formation of some *p*-benzoquinone. The yields of these products were, however, very low, $G \sim 0{\cdot}1$ (molecules/100 ev), and therefore could contribute only relatively little to the overall material balance.

On addition of 2 : 4-dinitrophenylhydrazine to the irradiated benzene solution, an orange-red precipitate was readily formed. This was observed in solutions irradiated with doses as low as $1{\cdot}25 \times 10^{-6}$ ev/***N*** per ml. and thus appeared to be derived from a primary product of irradiation. This hydrazone gave a violet-blue colour with alcoholic sodium hydroxide and was in many respects identical with the corresponding product obtained in Stein and Weiss's neutron irradiations; similarly, a *p*-nitrophenylhydrazone was obtained. We have been unable to prove unequivocally that mucondialdehyde is, in fact, the radiation product responsible for hydrazone formation : of the various substances examined, however, this dialdehyde fits the experimental observations most closely (*q.v.*). The yield was relatively small; estimated from the weight of the bishydrazones, this corresponded to a value of the order of $G \sim 0{\cdot}2$.

When aqueous solutions were irradiated *in vacuo*, on the other hand, no reaction with 2 : 4-dinitro- or *p*-nitro-phenylhydrazine was observed. This suggests that the more complex chemical changes are intimately connected with the participation of molecular oxygen in the radical processes and it is not unlikely that this may be due to the formation, in the first instance, of organic peroxy-radicals leading to a hydroperoxide from which water can be eliminated to give the dialdehyde :



A somewhat parallel case has been observed in the irradiation of aqueous solutions of tryptophan; [6] here it has been shown that opening of the indole ring occurs with the formation of formylkynurenine and that the presence of molecular oxygen in solution is essential.

It is confirmed that phenol is the major product ($G = 2{\cdot}2$) in the irradiation, with *X*-rays, of aqueous benzene containing oxygen; nevertheless, any interpretation of the radiation-induced oxidation should take into account these other chemical transformations.

Experimental

Irradiations.—Solutions were irradiated with unfiltered *X*-rays generated by a Victor Maximar therapy tube operating at 200 kv and 15 ma, by the technique previously described.[7] The dose rate was $3{\cdot}3 \times 10^{17}$ ev/***N*** per ml., $G_{Fe^{3+}}$ being taken as 15·5. Saturated solutions of benzene were prepared from "AnalaR" grade benzene and triply distilled water; these were then saturated with oxygen.

Nitrophenylhydrazone Derivatives.—The appropriate reagent was added to the irradiated solution and the mixture set aside until precipitation was complete (24 hr.). The precipitates were centrifuged off, washed, dried, dissolved in petrol–benzene (50 : 50, v/v), and chromatographed on acid-washed alumina. The eluting solvents were graded through the series petrol–benzene, benzene, and benzene–ether. The absorption spectrum of each eluate fraction was determined in spectroscopically pure ethanol by use of a "Unicam" spectrophotometer.

With dinitrophenylhydrazones, this method yielded one main and three subsidiary bands. Fig. 1(*a*) shows the visible spectrum of the major component, exhibiting two maxima; on very slow chromatography, a partial (though still poor) resolution was obtained, showing the major component to be a mixture of two closely related substances having maxima at 400 and 450 mμ, severally. Fig. 1, in addition, gives the spectrum of mucondialdehyde bis-2 : 4-dinitrophenylhydrazone (prepared from authentic mucondialdehyde kindly supplied by Professor F. G.

[5] Riley, *J. Amer. Chem. Soc.*, 1950, **72**, 5782.
[6] Jayson, Scholes, and Weiss, *Biochem. J.*, 1954, **57**, 386.
[7] Farmer, Stein, and Weiss, *J.*, 1949, 3241.

Fischer) and also that of the corresponding derivative of *p*-benzoquinone, both of which were purified by the above chromatographic procedure; resemblance between the spectra of these last two compounds and that of the first component of the radiation product is apparent. On the other hand, the possibility of the presence of *o*-benzoquinone was eliminated by the vast difference in absorption spectra of its dinitrophenylhydrazone from that of the radiation product. Similar experiments likewise eliminated 2-phenylbenzoquinone and diphenoquinone.

Chromatography of the *p*-nitrophenylhydrazone on alumina gave a major band, the spectrum of which is given in Fig. 2(*a*). Here, in contrast to that of the dinitro-compound, only one peak was observed, this being at 445 mμ. Spectra (*b*) and (*c*) in Fig. 2 are those of the mononitrophenylhydrazones of mucondialdehyde and *p*-benzoquinone, respectively. In this case, the

FIG. 1. *Absorption spectra in ethyl alcohol of the* 2 : 4-*dinitrophenylhydrazine derivatives of*: (*a*) Irradiation product. (*b*) Mucondialdehyde (bis-2 : 4-dinitrophenylhydrazone). (*c*) *p*-Benzoquinone (*i.e.*, 4-hydroxy-2′ : 4′-dinitroazobenzene).

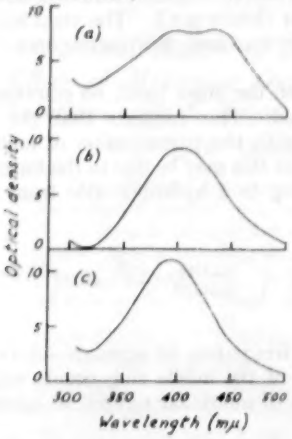
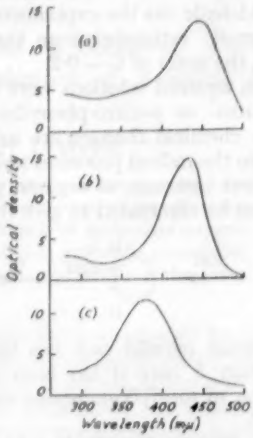


FIG. 2. *Absorption spectra in ethyl alcohol of the* p-*nitrophenylhydrazine derivatives of*: (*a*) Irradiation product. (*b*) Mucondialdehyde (bis-*p*-nitrophenylhydrazone). (*c*) *p*-Benzoquinone (*i.e.*, 4-hydroxy-4′-nitroazobenzene).



spectrum of the *p*-benzoquinone derivative (max. = 380 mμ) differs significantly from that of the derivative obtained from the irradiated solution. The main band of the irradiation product yielded some crystals, m. p. 265° (Fischer and Löwenberg[a] give 264° for the m. p. of mucondialdehyde bis-*p*-nitrophenylhydrazone).

Colour reactions of hydrazones with alcoholic sodium hydroxide.

	Irradiation product (main band)	Mucondialdehyde	*p*-Benzoquinone	*o*-Benzoquinone
2 : 4-Dinitrophenylhydrazone	Deep violet-blue	Deep violet-blue	Red-purple	Pale blue
p-Nitrophenylhydrazone ...	Cornflower-blue	Cornflower-blue	Red	Purple

Thus, of the various substances investigated, mucondialdehyde resembles most closely the radiation product, and colour reactions of the various hydrazones with alcoholic sodium hydroxide (see Table) support this deduction. The incomplete correspondence in the spectra may well be of stereochemical origin; it was unlikely that the synthetic sample (of unknown configuration) would necessarily be identical with that produced by irradiation of the benzene solutions.

Elementary analyses of the hydrazone fractions obtained by chromatography did not give satisfactory, reproducible results, the quantities available being too small.

Thanks are offered to the Director of the Atomic Energy Establishment, United Kingdom Atomic Energy Authority, for support and for permission to publish this paper, and to Dr. W. Taylor for help with some of the experiments.

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[a] Fischer and Löwenberg, *Ber.*, 1933, **66**, 665.

179. *A New Synthesis of Fluoro-ketones.*

By A. Sykes, J. C. Tatlow, and C. R. Thomas.

Trifluoroacetic acid, when treated with a Grignard reagent (RMgX; where R = Me, Et, Pr^i, Bu^n, Bu^t, Ph), afforded the corresponding ketone, CF_3·COR. Heptafluorobutyric acid and methylmagnesium iodide gave heptafluoropropyl methyl ketone. The ketones underwent haloform reactions, to give acids, R·CO_2H, identified as *S*-benzylthiuronium salts.

Several methods have been used hitherto for the synthesis of fluoro-ketones. Ester condensations, followed by hydrolyses of the derived β-keto-esters or β-diketones, have been employed most frequently.[1] For the synthesis of mixed aromatic fluoroalkyl ketones, Friedel–Crafts reactions have been utilised.[2] Fluoroacyl derivatives of reactive aromatic or heterocyclic compounds were made by Hoesch reactions.[3] Grignard-type syntheses involving fluorocarboxylic acid derivatives such as esters, acyl halides, etc., have been used for ketone production, but suffer from certain limitations. The chief of these is the formation, at the same time, of tertiary alcohols and, where the Grignard reagents have β-hydrogen atoms, secondary alcohols by reduction of any carbonyl groups present in the intermediates.[4] Very recently, it was shown by McBee, Pierce, and Meyer [5] that the reaction of Grignard reagents with perfluoro-nitriles proceeds normally, and hence may be used for ketone synthesis.

Experience in this Department has shown that the ester condensation route, though rather laborious, is satisfactory for the preparation of trifluoroacetone. However, when it was applied to the production of ethyl trifluoromethyl ketone, only poor yields of a very impure product were obtained. Accordingly, we considered possible alternative syntheses for fluoro-ketones, and it appeared likely that fluoro-acids themselves might react with Grignard reagents to give carbonyl compounds.

The acidic hydrogen of acids is of course removed by organomagnesium compounds in the well-known Zerewitinoff reaction. Alkanecarboxylic acids have long been known to give tertiary alcohols when treated with excess of organomagnesium halides,[6] but the process does not seem to have been used at all widely. However, ketones were obtained, in yields below 25%, by Salkind and Beburischwili [7] from sodium salts, and by Huston and Bailey [8] from acids themselves, though in the latter case tertiary alcohols were the major products. Highly fluorinated carbonyl compounds can give various quite well-defined compounds in which one carbon atom is linked to two oxygen atoms, *e.g.*, R·CF_2·CR′(OR″)$_2$. The stabilities of these relative to the hydrocarbon-type analogues are greatly enhanced by the presence of the electronegative fluorine substituents. For a reaction between a fluoro-acid and a Grignard reagent, it seemed possible that, after the former had undergone elimination of the active hydrogen and addition to the carbonyl group, the resulting complex might resist further reaction, in particular any replacement of oxygen-containing functions (such as O·MgX).

This supposition was confirmed experimentally. Anhydrous trifluoroacetic acid reacted readily with a number of Grignard reagents (RMgX; R = Me, Et, Pr^i, Bu^n, Bu^t, Ph) to give, after decomposition of the intermediate complexes in the usual way, the corresponding ketones (CF_3·COR), in reasonable yields (40—60%). Similarly, heptafluorobutyric acid and methylmagnesium iodide afforded heptafluoropropyl methyl ketone.

[1] *Inter alia*: (*a*) Swarts, *Bull. Acad. roy. Belg.*, 1927, **13**, 175; Darrall, Smith, Stacey, and Tatlow, *J.*, 1951, 2329; (*b*) Henne, Newman, Quill, and Staniforth, *J. Amer. Chem. Soc.*, 1947, **69**, 1819; (*c*) Nes and Burger, *ibid.*, 1950, **72**, 5409; (*d*) Barkley and Levine, *ibid.*, 1953, **75**, 2059; McBee, Pierce, Kilbourne, and Wilson, *ibid.*, p. 3152.

[2] Simons and Ramler, *ibid.*, 1943, **65**, 389; Simons, Black, and Clark, *ibid.*, 1953, **75**, 5621.

[3] Whalley, *J.*, 1951, 665; 1954, 1651.

[4] (*a*) Campbell, Knobloch, and Campbell, *J. Amer. Chem. Soc.*, 1950, **72**, 4380; McBee, Pierce, *et al.*, *ibid.*, 1952, **74**, 1736; 1953, **75**, 2324; 1955, **77**, 83; (*b*) Haszeldine, *J.*, 1953, 1748; 1954, 1273.

[5] McBee, Pierce, and Meyer, *J. Amer. Chem. Soc.*, 1955, **77**, 917.

[6] Grignard, *Compt. rend.*, 1904, **138**, 152.

[7] Salkind and Beburischwili, *Ber.*, 1909, **42**, 4500.

[8] Huston and Bailey, *J. Amer. Chem. Soc.*, 1946, **68**, 1382.

Gas–liquid partition chromatographic examination [9] of the ketones showed that they were either pure or contained only traces of impurities. Preparative-scale gas-chromatographic separation [9] afforded a ready means of removing the contaminants and giving completely pure products, except in the case of *iso*propyl trifluoromethyl ketone. The presence of these very minor constituents in certain cases does not imply that these ketones were particularly impure compared with volatile synthetic products in general. The gas-chromatographic technique, because of its sensitivity, can reveal the presence of very minor components, that would otherwise remain undetected and often do not introduce observable errors in elementary analyses. In relatively large-scale work a second fractional distillation will usually remove such impurities; this was so for some of the ketones. Preparative-scale gas–liquid chromatography, however, is an excellent method for purification of quantities smaller than can be handled in orthodox fractional distillation columns.

The ketonic products were characterised as 2 : 4-dinitrophenylhydrazones. Also, on treatment of the ketones with aqueous alkali, the usual haloform cleavage occurred with the production of carboxylic acids ($R{\cdot}CO_2H$) and presumably the fluorohydrocarbon (CHF_3 or C_3HF_7). The acids were identified mainly as *S*-benzylthiuronium salts (see Berger [10] for observations on the melting points of these salts). On elemental analysis the lower-boiling ketones gave erratic results for carbon, apparently owing to failure of the analytical method in these cases.

Dibutyl ether was used as the solvent in those Grignard syntheses yielding a product which had b.p. $<100°$, to simplify the isolation.[11] The best yields of ketones were obtained when about 2·5 mol. of Grignard reagent (for 1 mol. of acid) were used in the reaction. No improvement was effected by the addition of the Grignard reagent to the fluoro-acid. Small amounts of material with b. p. greater than that of the ketone were found in each case but we have not as yet identified these by-products.

The mechanism of the addition of Grignard reagents to carbonyl groups is generally considered to involve the formation of a 1 : 1 complex of the organometallic derivative and the carbonyl compound, which is then attacked by a second molecule of the Grignard reagent.[12, 4b] Our results appear to conform with this idea, on the assumption [11, 13] that Grignard reagents are formed from methyl and ethyl iodide in yields of *ca.* 90%. Yields of the methyl and ethyl ketones, from 0·1 mole of trifluoroacetic acid, were 25—30% when 0·18 mole of Grignard reagent was used, 35—40% with 0·2 mole of Grignard reagent, and 50—60% with 0·225—0·30 mole of Grignard reagent. In these reactions, the acid was added to the organometallic compound, *i.e.*, an excess of the latter was present in the early stages. When the Grignard reagent (0·18 mole) was added to the acid (0·1 mole), only 12% of ketone was obtained, though with 0·27 mole of the Grignard reagent *ca.* 50% of ketone was formed. Thus, after allowance for the Grignard reagent (0·1 mole) which reacts with the active hydrogen, more than 0·1 mole seems to be required for the addition.

As mentioned earlier, fluoro-carbonyl compounds are very susceptible to reduction by organomagnesium compounds having β-hydrogen atoms. If ketones can be formed as intermediates in syntheses by using such reagents, the end-products isolated are often secondary alcohols, formed by this reduction.[4a] *iso*Propylmagnesium bromide and other branched-chain Grignard reagents are the most powerful reducing agents in this type of process, and Pierce, Siegle, and McBee [14] have utilised this to provide a useful extension of the general reaction. By treatment of fluoro-esters (*e.g.*, $CF_3{\cdot}CO_2Me$) with a mixture of Grignard reagents (*e.g.*, $MeMgX + Pr^iMgX$) they obtained secondary alcohols (*e.g.*, $CF_3{\cdot}CHMe{\cdot}OH$) from Grignard reagents which contained no β-hydrogen atoms and would normally react further to give tertiary alcohols. The secondary alcohols may of course be oxidised back to ketones, and we have made ethyl trifluoromethyl ketone, identical with the other specimen, in this way. In contrast with the behaviour described above, however, the reactions of trifluoroacetic acid with *iso*propyl- and *tert.*-butyl-magnesium halides have

[9] Evans and Tatlow, *J.*, 1955, 1184.
[10] Berger, *Acta Chem. Scand.*, 1954, **8**, 427.
[11] Marvell, Blomquist, and Vaughn, *J. Amer. Chem. Soc.*, 1928, **50**, 2910.
[12] (*a*) Swain and Boyles, *ibid.*, 1951, **73**, 870; (*b*) Mosher and Combe, *ibid.*, 1950, **72**, 3994.
[13] Gilman and McCracken, *ibid.*, 1923, **45**, 2462; Gilman and Meyers, *ibid.*, p. 159.
[14] Pierce, Siegle, and McBee, *ibid.*, 1953, **75**, 6324.

given ketones, though in the latter case in yields rather lower than those obtained from straight-chain compounds. The accepted mechanism for the reduction of carbonyl compounds by Grignard reagents involves an internal rearrangement of the 1 : 1 Grignard–carbonyl complex.

In the cases of fluorine-free compounds, if magnesium bromide was used to form a complex with the carbonyl group the amount of reduction was considerably less.[12a] McBee, Pierce, and Meyer,[4a] however, found no evidence that fluoro-carbonyl compounds gave complexes of this type, though the presence of magnesium bromide in a Grignard synthesis did give rise to less reduction. In our reactions, the addition of the magnesium bromide–ether complex seemed to have no effect. The isolation of appreciable yields of ketones from the reactions of branched-chain Grignard reagents with fluoro-acids shows that the groups adjacent to a fluoro-carbonyl function can have profound influences on its behaviour with organomagnesium compounds. It is possible that the known ability of perfluoro-acids to form addition compounds with ethers,[15] which presumably means that the acids are already bound as complexes, is of importance in this aspect of the reaction.

Our general process for ketone synthesis possesses certain advantages; it is simple, it uses the free acids (usually the basic raw materials of each series), and it may be applied to branched-chain compounds. Further investigations, such as the use of other organometallic compounds, may well lead to improvements. Since this work was done, McGrath and Levine [16] have in fact described the preparation of ketones from perfluoro-acids and organolithium compounds. A preliminary report of the present investigation has been published elsewhere.[17]

Experimental

Preparation of 1 : 1 : 1-*Trifluoroacetone.*—Magnesium (7·2 g.) was treated with methyl iodide (42·6 g.) in di-*n*-butyl ether (75 c.c.) to give, in the usual way, methylmagnesium iodide (*ca.* 0·3 mole). The reaction vessel was surrounded by a water-bath at about 10° while trifluoroacetic acid (11·4 g., 0·1 mole) in di-*n*-butyl ether (25 c.c.) was added, dropwise, with continuous stirring. The stirring was continued for a further 90 min. at 10—15°. At 0°, and with a condenser cooled with solid carbon dioxide–alcohol attached to the system, water (25 c.c.) was added, followed by 7N-hydrochloric acid (75 c.c.). The aqueous layer was separated, extracted three times with di-*n*-butyl ether, and the combined ethereal solutions fractionally distilled (1′ column, packed with Dixon gauze spirals), to give 1 : 1 : 1-trifluoroacetone (6·3 g., 56%), b. p. 21·5—22·5°.

Under similar conditions, the following results were obtained by varying the amounts of Grignard reagent used, the figures given being in each case the quantity of methyl iodide used (mole) and the yield of trifluoroacetone (%), respectively: 0·20, 33; 0·22, 37; 0·25, 56; 0·27, 57. When the Grignard reagent (from 0·2 mole of methyl iodide) was added to trifluoroacetic acid (0·1 mole), the ketone was obtained in 12% yield only. When the acid (0·1 mole) was added to the methylmagnesium iodide (from 0·30 mole of methyl iodide) and the mixture stirred at 10—15° for 19 hr., 65% of trifluoroacetone was obtained. From a similar experiment in which the mixture was heated at 75—80° for 2 hr., the ketone was obtained in 62% yield.

The semicarbazone, prepared in the usual way, had m. p. and mixed m. p. 127—128° (Swarts [18] gave m. p. 127°) (Found: C, 28·5; H, 3·4. Calc. for $C_4H_6ON_3F_3$: C, 28·4; H, 3·6%). The ketone also gave, in the usual manner, the 2 : 4-dinitrophenylhydrazone, m. p. 137·5—138·5° (Found: C, 36·8; H, 2·5; F, 19·1. Calc. for $C_9H_7O_4N_4F_3$: C, 37·0; H, 2·4; F, 19·5%). Henne *et al.*[15] gave m. p. 139°.

Ethyl Trifluoromethyl Ketone.—Ethylmagnesium iodide (from ethyl iodide, 0·3 mole) was treated with trifluoroacetic acid (0·1 mole) as described above. After the Grignard complex had been decomposed, the ethereal layer was separated, dried ($MgSO_4$), and fractionated (6″ column), and the combined crude products from two such experiments were refractionated (1′ column), to give ethyl trifluoromethyl ketone (52%), b. p. 45—45·5°/741 mm., n^{16} 1·3069 (Found: F, 45·2. Calc. for $C_4H_5OF_3$: F, 45·2%). Barkley and Levine [1d] gave b. p. 44—45°/738 mm.

Under similar conditions, direct addition of trifluoroacetic acid (0·1 mole) to the Grignard

[15] Hauptschein and Grosse, *J. Amer. Chem. Soc.*, 1951, **73**, 5139.
[16] McGrath and Levine, *ibid.*, 1955, **77**, 3656.
[17] Sykes, Tatlow, and Thomas, *Chem. and Ind.*, 1955, 630.

reagent gave the ketone in yields of 24% (from ethyl iodide, 0·20 mole), 47% (from ethyl iodide, 0·25 mole), and 45% (from ethyl iodide, 0·40 mole). When the acid (0·1 mole) was added to ethylmagnesium iodide (from 0·30 mole of iodide), and the mixture was heated at 80—90° for 2 hr. the yield of ketone was 48%. From a similar experiment in which the reaction mixture was kept at 10—15° for 21 hr., the yield was 54%. Reverse addition of the Grignard reagent to the acid, followed by a reaction time of 90 min., gave yields of ketone of 12% (from 0·20 mole of iodide) and 52% (from 0·3 mole of iodide).

The *semicarbazone*, prepared in the usual manner, had m. p. 128—129° (Found: C, 33·0; H, 4·0; F, 30·8. $C_5H_8ON_3F_3$ requires C, 32·8; H, 4·4; F, 31·1%). The 2:4-dinitrophenylhydrazone had m. p. 89·5—91° (Found: C, 39·4; H, 2·8. Calc. for $C_{10}H_9O_4N_4F_3$: C, 39·2; H, 3·0%); Barkley and Levine [14] gave m. p. 91—92°.

This ketone (2·7 g.) was heated with aqueous 2N-sodium hydroxide (10 c.c.) at 50—60° for 1 hr. After acidification with hydrochloric acid (to pH 4), aqueous *S*-benzylthiuronium hydrochloride was added. The precipitate was recrystallised from water, to give *S*-benzylthiuronium propionate (2·7 g., 53%), m. p. and mixed m. p. 153—154° (Found: C, 55·3; H, 6·9. Calc. for $C_{11}H_{16}O_2N_2S$: C, 55·0; H, 6·7%). Berger [10] gave m. p. 153°.

*iso*Propyl *Trifluoromethyl Ketone*.—*iso*Propylmagnesium bromide (from 0·6 mole of bromide) reacted with trifluoroacetic acid (0·2 mole) as described earlier. The ethereal solution, obtained as before, was dried ($MgSO_4$) and distilled (1′ column). The combined crude products from two such experiments were refractionated (1′ column), to give the *ketone* (51%), b. p. 58° (Found: F, 39·7. $C_5H_7OF_3$ requires F, 40·7%).

This sample of ketone showed no impurities in an analytical gas-chromatographic tube filled with a dinonyl phthalate–kieselguhr. However, with a polyethylene glycol–kieselguhr packing, a minor impurity (<2%) was detected. This could not be separated on the large-scale chromatographic tube, which has the ester packing (a preparative-scale tube with the polyglycol packing was not available). The impurity may well have been 2:3-dimethylbutane (b. p. 58°).

The product afforded in the usual way a 2:4-*dinitrophenylhydrazone* (66%), m. p. 80·5—81·5° (Found: C, 41·4; H, 3·5; F, 17·4. $C_{11}H_{11}O_4N_4F_3$ requires C, 41·25; H, 3·5; F, 17·8%).

The ketone was hydrolysed with alkali as described above, to give *iso*butyric acid, which was identified as its *p*-bromophenacyl ester, m. p. and mixed m. p. 75·5° (mixed m. p. with *p*-bromophenacyl *n*-butyrate 46—48°) and as its *S*-benzylthiuronium salt (33%), m. p. and mixed m. p. 145—146° (Found: C, 56·6; H, 6·8. Calc. for $C_{12}H_{18}O_2N_2S$: C, 56·7; H, 7·1%), for which Berger [10] gave m. p. 143°.

n-*Butyl Trifluoromethyl Ketone*.—*n*-Butylmagnesium bromide (from *n*-butyl bromide, 0·3 mole) was treated with trifluoroacetic acid (0·1 mole) as described previously. The ethereal solution was dried ($MgSO_4$) and fractionated (1′ column), to give n-*butyl trifluoromethyl ketone* (63%), b. p. 89·5—90·5°, n^{19} 1·3485 (Found: C, 47·2; H, 6·1. $C_6H_9OF_3$ requires C, 46·8; H, 5·9%). A 2:4-*dinitrophenylhydrazone* (76%), prepared in the usual way, had m. p. 48·5—49° (Found: C, 43·1; H, 3·8; F, 16·8. $C_{12}H_{13}O_4N_4F_3$ requires C, 43·1; H, 3·9; F, 17·0%).

Alkaline hydrolysis of the ketone, as previously described, gave *n*-valeric acid, identified, in the usual manner, as its *S*-benzylthiuronium salt (52%), m. p. and mixed m. p. 150—150·5° (Found: C, 58·5; H, 7·4. Calc. for $C_{13}H_{20}O_2N_2S$: C, 58·2; H, 7·5%). Berger [10] gave m. p. 149°.

tert.-*Butyl Trifluoromethyl Ketone*.—*tert*.-Butylmagnesium bromide (from *tert*.-butyl bromide, 0·6 mole) was treated with trifluoroacetic acid (0·2 mole) as described above. By the standard procedure, the ethereal solution was obtained, dried ($MgSO_4$), and fractionated (1′ column), to give the desired compound (28%) which contained a little impurity. Large-scale gas-chromatography afforded pure tert.-*butyl trifluoromethyl ketone* (65% recovery), b. p. 69—70°, n^{20} 1·3515 (Found: F, 36·9. $C_6H_9OF_3$ requires F, 37·0%). An impurity, m. p. 99—100°, isolated from the chromatographic separation appeared to be 2:2:3:3-tetramethylbutane.

In the usual way, a 2:4-*dinitrophenylhydrazone*, m. p. 121—122°, was prepared (Found: C, 43·5; H, 3·6%).

Hydrolysis of the ketone, by the standard method, gave pivalic acid, identified as its *S*-benzylthiuronium salt, m. p. and mixed m. p. 146·5—147° (mixed m. p. with *S*-benzylthiuronium *n*-valerate, 133—137°) (Found: C, 58·3; H, 7·3%).

Phenyl Trifluoromethyl Ketone.—Phenylmagnesium bromide (from bromobenzene, 0·3 mole) in diethyl ether (75 c.c.) was treated with trifluoroacetic acid (0·1 mole) in diethyl ether (25 c.c.). The complex was decomposed by the standard procedure. The ethereal solution was dried ($MgSO_4$) and fractionated (6″ column), to give, after removal of the ether and benzene, trifluoroacetophenone (62%), b. p. 152—153°/759 mm., n^{20} 1·4597. The 2:4-dinitrophenylhydrazone

(75%) had m. p. 106—107·5° (Found : C, 47·7; H, 2·7; F, 16·3. Calc. for $C_{14}H_9O_4N_4F_3$: C, 47·5; H, 2·6; F, 16·1%). Simons *et al.*[2] gave b. p. 152°/730 mm., n_D^{20} 1·4583, for the ketone and m. p. 94·5—95·5° for the derivative.

The ketone (1·20 g.) was heated with aqueous 2N-sodium hydroxide (10 c.c.) for 30 min. at 80°. Acidification of the solution gave benzoic acid (0·76 g., 95%), m. p. and mixed m. p. 121—122°.

Heptafluoropropyl Methyl Ketone.—Methylmagnesium iodide (from methyl iodide, 0·15 mole) was treated with heptafluorobutyric acid (0·05 mole) as described before. The ethereal solution was dried ($MgSO_4$) and distilled, to give slightly impure heptafluoropropyl methyl ketone (41%), b. p. 63—64°. Large-scale gas-chromatography gave a pure sample (96% recovery) (Found : F, 62·4. Calc. for $C_5H_3OF_7$: F, 62·7%). The 2 : 4-dinitrophenylhydrazone (82%), obtained by the usual method, had m. p. 75·5° (Found : C, 33·8; H, 1·5; F, 34·3. Calc. for $C_{11}H_7O_4N_4F_7$: C, 33·7; H, 1·8; F, 33·9%). McBee, Pierce, and Marzluff [18] gave b. p. 63·5° for the ketone, and m. p. 76·5° for the derivative.

Hydrolysis of the ketone and treatment of the solution by the standard procedure gave *S*-benzylthiuronium acetate, m. p. and mixed m. p. 134—135° (Found : C, 53·3; H, 6·1. Calc. for $C_{19}H_{14}O_2N_2S$: C, 53·1; H, 6·2%). Berger [10] gave m. p. 136°.

*Reaction of Trifluoroacetic Acid with Methylmagnesium Iodide in the Presence of Magnesium Bromide–Di-*n*-butyl Ether Complex.*—Magnesium (2·43 g.) was stirred in di-*n*-butyl ether (50 c.c.) while bromine (16·0 g.) was added dropwise. When the colour of the bromine had disappeared, trifluoroacetic acid (11·4 g.) in di-*n*-butyl ether (25 c.c.) was added dropwise with continuous stirring. After 1 hr., methylmagnesium iodide (*ca.* 0·2 mole), prepared from methyl iodide (31·3 g.) in di-*n*-butyl ether (65 c.c.), was added slowly, with continuous stirring, whilst the flask was cooled in a water-bath (*ca.* 10°). After 16 hr. at 10—15° the complex was decomposed with water (20 c.c.) and 7N-hydrochloric acid (75 c.c.). Isolation as usual afforded 1 : 1 : 1-trifluoroacetone (4·6 g., 42%), b. p. 19·8—23°.

Reaction of Trifluoroacetic Acid with iso*Propylmagnesium Bromide in the Presence of Magnesium Bromide–Di-*n*-butyl Ether Complex.*—Magnesium (0·1 g.-atom) was treated with bromine (0·1 mole) and trifluoroacetic acid (0·1 mole) was added, followed by *iso*propylmagnesium bromide (*ca.* 0·24 mole), prepared from *iso*propyl bromide (0·3 mole). After 90 min. the complex was decomposed to give *iso*propyl trifluoromethyl ketone (40%), b. p. 49—58°. The 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 80°.

Oxidation of 1 : 1 : 1-*Trifluorobutan-2-ol.*—This secondary alcohol (5·5 g.), prepared by the method of Pierce, Siegle, and McBee,[14] was heated on a water-bath with 50% sodium dichromate solution (25 c.c.) and concentrated sulphuric acid (10 c.c.). Ethyl trifluoromethyl ketone (3·8 g., 70%) was collected in a solid carbon dioxide–ethyl alcohol trap. Gas-chromatographic analysis showed a peak identical with that given by the other sample. In the usual way the ketone gave the 2 : 4-dinitrophenylhydrazone (87%), m. p. and mixed m. p. 90—91·5°.

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EDGBASTON, BIRMINGHAM, 15. [*Received, July 14th,* 1955.]

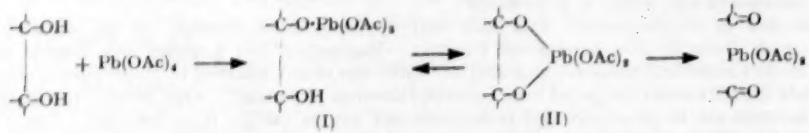
[18] McBee, Pierce, and Marzluff, *J. Amer. Chem. Soc.*, 1953, **75**, 1609.

180. *The Mechanisms of Oxidative Fission of Stereoisomeric 1 : 2-Glycols.*

By (Miss) P. Levesley, William A. Waters, and A. N. Wright.

Evidence is brought forward to show that the oxidation of 1 : 2-glycols by manganic pyrophosphate and by lead tetra-acetate does not always proceed through the initial formation of a cyclic organometallic complex. In particular, attention is directed to the fact that *trans*-1 : 2-dimethyl*cyclo*pentane-1 : 2-diol is oxidised more easily than *cis-cyclo*hexane-1 : 2-diol or *cis*-1 : 2-dimethyl*cyclo*hexane-1 : 2-diol. Exploratory studies of glycol oxidation by manganic pyrophosphate indicate that more than one reaction mechanism may be concerned in oxidative glycol fissions. Stereochemical significance should not therefore be attached to simple measurements of relative rates of oxidation.

It is widely thought that the oxidative fission of 1 : 2-glycols by reagents such as lead tetra-acetate, periodic acid, aryl iodoacetates [1] and sodium bismuthate [2] occurs by formation of an intermediate cyclic complex [*e.g.*, (II)] within which an electron redistribution may easily occur by bond fissions which may be written as heterolytic [2,3] or homolytic [4] processes according to choice, no discrimination between these alternatives by experimental means being possible. The evidence depends on observations [1,5,6] that in both the *cyclo*pentane and *cyclo*hexane series *cis*-1 : 2-glycols are cleaved more rapidly than their *trans*-isomers. This stereochemical concept has been applied by Prelog and his colleagues [7] in



assigning conformations to the isomeric 1 : 2-glycols of larger *cyclo*alkane rings. However, though cyclic condensation products of 1 : 2-glycols with ketones, and with boric acid, have been prepared no one has, as yet, isolated the cyclic intermediate which is thought to be involved in any oxidative glycol fission.

For oxidations by lead tetra-acetate Criegee and his colleagures [5,8] have suggested that the bimolecular [9] rate-determining stage may really be that of the formation of an uncyclised lead compound (I), analogous to a product $MeO{\cdot}Pb(OAc)_2{\cdot}OH$ obtained from lead tetra-acetate and slightly damp methanol. They have pointed out that in these oxidations slight changes in the composition of the solvent produces changes of the reaction velocity which are far too great to be accounted for by the intramolecular cyclisation (I ⟶ II), and the same idea has been developed further by Pausacker *et al.*[10,11] who suggested that hydrogen bonding between vicinal hydroxyl groups could greatly affect the ease with which a 1 : 2-glycol might give a product of type (I) and that no cyclic lead compound need be formed. For oxidations by aryl iodosoacetates the same considerations apply.[1,11]

With periodic acid oxidations the structural effects are much less strongly marked, for both *cis*- and *trans*-glycols can be oxidised and the pH of the solution seems to be the

[1] Criegee and Beuker, *Annalen*, 1939, **541**, 218.
[2] Rigby, *J.*, 1950, 1907.
[3] Criegee, *Annalen*, 1948, **560**, 132.
[4] Dewar, "The Electronic Theory of Organic Chemistry," Oxford, 1949, pp. 276—277.
[5] Criegee, Kraft, and Rank, *Annalen*, 1933, **507**, 159.
[6] Criegee, Büchner, and Walther, *Ber.*, 1940, **73**, 571.
[7] Prelog, Schenker, and Günthard, *Helv. Chim. Acta*, 1952, **35**, 1598.
[8] Criegee and Büchner, *Ber.*, 1940, **73**, 563.
[9] Bell, Sturrock, and Whitehead, *J.*, 1940, 82.
[10] Cordner and Pausacker, *J.*, 1953, 102.
[11] Pausacker, *J.*, 1953, 107.

main rate-controlling factor. Kinetic studies however indicate that some complex formation does precede the actual carbon–carbon bond fission.[12] Again with sodium bismuthate there is no outstanding difference between the rates of oxidation of isomeric *cis*- and *trans-cyclo*hexane-1 : 2-diols, though few studies have as yet been made with this reagent.[2]

The recent kinetic study by Drummond and Waters [13] of the oxidation of pinacol by manganic pyrophosphate indicated that chelate-ring formation, with a pinacol molecule displacing a bidentate pyrophosphate group,

$$\text{Pinacol} + \text{Mn}(\text{H}_3\text{P}_2\text{O}_7)_3^{3-} \rightleftharpoons \text{Mn}(\text{Pin})(\text{H}_3\text{P}_2\text{O}_7)_2^{-} + \text{H}_3\text{P}_2\text{O}_7^{2-}$$

was a necessary initial step in this oxidation, for the reaction velocity was proportional to [Glycol]/([$H_2P_2O_7^{2-}$] + *a*[Glycol]) as would be the case if the rate-determining stage of the reaction sequence were the slow breakdown of the complex $Mn(Pin)(H_2P_2O_7)_2^-$. Oxidations by manganic pyrophosphate of typical α-hydroxy-acids [14] and of malonic [15] and pyruvic [16] acid also seem to involve chelate-ring formation, though the oxidations of simple aldehydes [17] and ketones [16] can be represented as direct electron abstractions from enols that clearly cannot be bidentate chelating agents. Since the equilibrium constant for chelate-ring formation from a 1 : 2-glycol (cf. the reaction scheme above) should be closely connected with its stereochemical conformation it was considered that kinetic studies of the ease of oxidative fission of stereoisomeric 1 : 2-glycols by manganic pyrophosphate would yield data of superior quantitative value to those provided by any of the kinetic measurements of glycol fission recorded hitherto.

Exploratory work showed that, as expected, manganic pyrophosphate oxidised methyl α-D-mannoside more rapidly than the all-*trans* methyl α-D-glucoside, but that the oxidation of *trans*-1 : 2-dimethyl*cyclo*hexane-1 : 2-diol did not quite parallel that of pinacol, for it was evidently a reaction of first order with respect to the glycol concentration. The work has therefore been continued. The rates of oxidation of the *cis*- and the *trans*-isomers of *cyclo*hexane-1 : 2-diol and 1 : 2-dimethyl*cyclo*hexane-1 : 2-diol and of *trans*-1 : 2-dimethyl-*cyclo*pentane-1 : 2-diol have been compared. Fig. 1 shows oxidation curves obtained at 40° with equimolar concentrations of these glycols and manganic pyrophosphate at pH 0·2, and Fig. 2 shows similar curves obtained with lead tetra-acetate in glacial acetic acid at 25°. The outstanding features of the manganic pyrophosphate oxidations are (i) that *trans*-1 : 2-dimethyl*cyclo*pentane-1 : 2-diol is oxidised so easily and (ii) that *cis*-1 : 2-dimethyl*cyclo*-hexane-1 : 2-diol is oxidised much more slowly than is its *trans*-isomer; however, as expected, *cis-cyclo*hexane-1 : 2-diol is oxidised more rapidly than the *trans*-compound, but consumes four, and not two, equivalents of the oxidant. With lead tetra-acetate the relative reactivities of these compounds are different: with both pairs of *cyclo*hexanediols the *cis*-isomer is oxidised more rapidly, but again *trans*-1 : 2-dimethyl*cyclo*pentane-1 : 2-diol is oxidised very easily.

The observations with *trans*-1 : 2-dimethyl*cyclo*pentane-1 : 2-diol were unexpected, for, though in a few compounds a *cyclo*hexane ring is able to pucker sufficiently to allow a *trans*-1 : 2-diol to condense to a 5-membered ring derivative,[18] it was thought that the *cyclo*pentane ring would be so much more rigidly planar that *trans*-hydroxyl groups could not easily be forced into sufficiently close proximity for junction by any single atom. Ring complexes of vicinal *trans*-diols in the *cyclo*pentane series (*e.g.*, furanoses) with boric acid or acetone are unknown, though Barrett and Linstead [19] have made both *cis*- and *trans-bicyclo*[3 : 3 : 0]-octanes and -octanones, and Owen and Peto [20] the corresponding 3-oxa- and 3-thia-compounds. Nevertheless the successful *trans*-union of two 5-membered rings

[12] Price and Knell, *J. Amer. Chem. Soc.*, 1942, **64**, 552; Price and Kroll, *ibid.*, 1938, **60**, 2726; Duke, *ibid.*, 1947, **69**, 3054; Buist and Bunton, *J.*, 1954, 1406.
[13] Drummond and Waters, *J.*, 1953, 3119.
[14] Levesley and Waters, *J.*, 1955, 217.
[15] Drummond and Waters, *J.*, 1954, 2456.
[16] *Idem*, *J.*, 1955, 497.
[17] *Idem*, *J.*, 1953, 440.
[18] Angyal and Macdonald, *J.*, 1952, 686.
[19] Barrett and Linstead, *J.*, 1935, 436.
[20] Owen and Peto, *J.*, 1955, 2383.

involves considerable intramolecular strain, for the heat of combustion of the *trans*-dicyclic ketone is 6·8 kcal. more than that of its *cis*-isomer.[19]

However our present measurements with *trans*-1 : 2-dimethyl*cyclo*pentane-1 : 2-diol are in full accord with results reported several years ago by Criegee and his colleagues [5,6] which are collected in Table 1. These show that the activation energy for the oxidation of *trans-cyclo*pentane-1 : 2-diol is in fact less than that required for either of the 1 : 2-*cyclo*hexanediols and that the *trans*-diphenylacenaphthenediol, in which the naphthalene

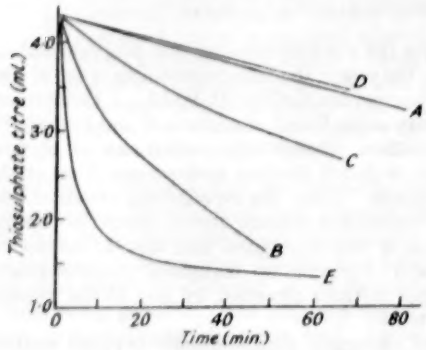


FIG. 1. *Oxidations with manganic pyrophosphate.*
pH 0·20. Temp. 40°.
Initial [Glycol] 5·9 × 10^{-3}M.
Initial [Mn^{III}] 1·7 × 10^{-2}M.
[Pyrophosphate] 0·119M.

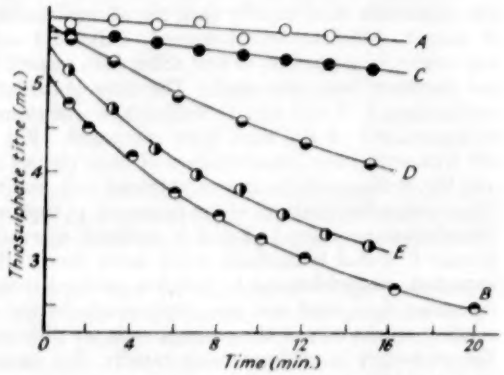


FIG. 2. *Oxidations with lead tetra-acetate.*
Glacial acetic acid solution at 25°.
Initial [Glycol] 4·93 × 10^{-3}M.
[Lead tetra-acetate] 2·65 × 10^{-2}M.

Curves A, trans-cyclo*Hexane*-1 : 2-*diol*.
Curves B, cis-cyclo*Hexane*-1 : 2-*diol*.
Curves C, trans-1 : 2-*Dimethyl*cyclo*hexane*-1 : 2-*diol*.
Curves D, cis-1 : 2-*Dimethyl*cyclo*hexane*-1 : 2-*diol*.
Curves E, trans-1 : 2-*Dimethyl*cyclo*pentane*-1 : 2-*diol*.

system confers rigidity on the 5-membered ring fused to it, is oxidised still more easily. Again *trans*-decalin-9 : 10-diol as well as its isomer can be oxidised at a reasonable rate to *cyclo*decanedione.[6]

Thus the results shown in Table 1 and in Figs. 1 and 2 give no basis for the view that stereochemical factors, *per se*, rather than polar factors connected with the electronic

TABLE 1. *Records of glycol oxidation by lead tetra-acetate.*[5,6,9]
(k in mole $l.^{-1}$ $min.^{-1}$; E in kcal. $mole^{-1}$)

Diol	*cis*		*trans*	
	k_{20}	E	k_{20}	E
*cyclo*Hexane-1 : 2-diol	5·04	20·5	0·224	21·4
*cyclo*Pentane-1 : 2-diol	40,000	—	12·8	19·8
Tetralin-1 : 2-diol	40·2	18·8	1·86	20·3
Indane-1 : 2-diol	27,800	—	0·467	20·9
7 : 8-Diphenylacenaphthene-7 : 8-diol	33,100	8·3	284	15·5
Decalin-9 : 10-diol	15·0	—	0·148	—

structures of neighbouring groups, are primarily responsible for observed changes of oxidation rate. Similar conclusions have been reached from computations of bond distances in cyclic 1 : 2-diols.[21]

Since glycol fission by manganic pyrophosphate has demonstrated that 1-electron transitions in which free radicals are formed can be involved in the oxidation process, attention may be directed to the observation [22] that glycol fission by chromyl chloride involves the 1-electron transition from Cr^{VI} to Cr^{V}, to the fact that hydroxyl radicals, which cannot promote cyclic complex formation, can effect some carbon–carbon bond fission of 1 : 2-glycols [23] and to evidence that some oxidations involving periodic acid involve 1-electron transitions.[24] Consequently homolytic oxidation mechanisms involving two successive 1-electron transitions, developing those vaguely indicated by Criegee [25] in 1935, outlined by Waters [26] in 1939, and advanced again by Cordner and Pausacker [10] in 1953, must be given serious consideration. If glycol fission is visualised as a two-stage process then the stages may be concerted (when current stereochemical ideas would indicate that *trans*-reaction might be favoured) or consecutive, passing through a transient radical intermediate, and predominantly controlled by the nature of the solvent.[10]

Whenever a series of consecutive reactions is involved it cannot safely be inferred that the same stage in the reaction sequence is rate-determining for each member of an isomeric, or homologous, series. It has only been possible for us to examine the reaction mechanisms of oxidation of cyclic 1 : 2-glycols in a preliminary way, but the results given in the following Experimental section show that with manganic pyrophosphate oxidation the rate-determining stage is not the same for all glycols and that no general correlation between stereochemical conformation and ease of oxidation should therefore be made. We suggest that theoretical deductions made from rate measurements of other glycol fission reactions should, pending thorough physicochemical studies, be viewed with similar scepticism, and that kinetic evidence of (glycol–oxidant) complex formation should not be taken as diagnostic of *cyclic* complex formation.

Experimental

Preparation of the Cyclic 1 : 2-*Glycols.*—(i) trans-1 : 2-*Dimethylcyclopentane*-1 : 2-*diol.* Ethyl 1-methyl-2-oxo*cyclo*pentanecarboxylate was converted in 65—70% yield by the method of Shive, Crouch, and Lochte [27] into 2-methyl*cyclo*pentanone which was treated with methylmagnesium iodide and then dehydrated to 1 : 2-dimethyl*cyclo*pentene. This olefin (10 g.) was oxidised to the *trans*-glycol by cold 30% hydrogen peroxide (20 ml.) and 99% formic acid (50 ml.) in 25% yield. After distillation in a vacuum this diol crystallised from light petroleum (b. p. 60—80°) and had m. p. 99—102°.

trans-1 : 2-Dimethyl*cyclo*hexane-1 : 2-diol, prepared similarly from 1 : 2-dimethyl*cyclo*hexene, had b. p. 78°/12 mm. and m. p. 92—93°, whilst *trans-cyclo*hexane-1 : 2-diol had m. p. 104° (dibenzoate, m. p. 94°).

(ii) *cis-cyclo*Hexane-1 : 2-diol was prepared in small quantity from the *trans*-monotoluene-*p*-sulphonate as described by Criegee and Stanger,[28] but in better quantity (yield 33%) by the oxidation at −15° to −20° of *cyclo*hexene with potassium permanganate in aqueous ethanol containing magnesium sulphate, as described by Clarke and Owen;[29] it had m. p. 98°. *cis*-1 : 2-Dimethyl*cyclo*hexane-1 : 2-diol was prepared by a similar oxidation of 1 : 2-dimethyl*cyclo*hexene following the detailed procedure of Meerwein,[30] which involves a purification with semicarbazide to remove 2 : 7-dioxo-octane. The final product had b. p. 102°/10 mm. and m. p. 50°.

Kinetic Measurements.—Measurements with manganic pyrophosphate were made by the procedure used by Drummond and Waters.[13] The steady reproducible values for the initial

[21] Kuhn, *J. Amer. Chem. Soc.*, 1954, **76**, 4323.
[22] Slack and Waters, *J.*, 1949, 594.
[23] Waters, *Nature*, 1946, **158**, 380.
[24] Symons, *J.*, 1955, 2794.
[25] Criegee, *Ber.*, 1935, **68**, 665.
[26] Waters, *J.*, 1939, 1805; *Trans. Faraday Soc.*, 1946, **42**, 185.
[27] Shive, Crouch, and Lochte, *J. Amer. Chem. Soc.*, 1941, **63**, 2983.
[28] Criegee and Stanger, *Ber.*, 1936, **69**, 2753.
[29] Clarke and Owen, *J.*, 1949, 318.
[30] Meerwein, *Annalen*, 1939, **542**, 123.

reaction rates showed that oxygen did not affect the reaction velocity. Tests with dinitrophenylhydrazine showed that *trans*-dimethyl-*cyclo*pentanediol and -*cyclo*hexanediol were oxidised to ketones but that *cis-cyclo*hexanediol was further oxidised to adipic acid. This confirmed measurements of the stoicheiometry of completed oxidations.

Lead tetra-acetate oxidations were carried out in glacial acetic acid at 25°, following the procedure of Cordner and Pausacker.[10] One batch of purified acetic acid was used for preparing all solutions.

Investigations of Reaction Orders for Glycol Oxidation by Manganic Pyrophosphate by Means of Initial-rate Measurements.—(a) *Oxidations of methyl* α-D-*pyranosides.* The results in Table 2

TABLE 2. *Oxidation of pyranosides.*

pH 0·04. Temp. 45·5°. Initial [Mn^{III}] 0·0135M. [P_2O_7] 0·109M.

Methyl α-D-*glucopyranoside.*

Initial concn. (10^{-3}M)	10·65	6·95	5·26	4·21	3·49	2·63	1·74	1·58	1·32	0·87	0·75
Initial rate (mole of Mn $l.^{-1}$ $hr.^{-1}$)	4·55	4·15	3·75	3·21	2·94	2·65	2·04	1·94	1·83	1·22	1·02

Methyl α-D-*mannopyranoside.*

Initial concn. (10^{-3}M)	1·58	0·83	0·65	0·53	0·42	0·35	0·29	0·26
Initial rate (mole of Mn $l.^{-1}$ $hr.^{-1}$)	1·58	1·08	0·92	0·80	0·74	0·61	0·54	0·48

show that the order with respect to the pyranoside is less than unity, particularly when the organic compound is present in excess. A reciprocal plot shows that the observed kinetic relationship is similar to that found for pinacol.[13]

(b) *Oxidations of* trans-1 : 2-*dimethylcyclopentane*-1 : 2-*diol.* Results showing the order with respect to the diol and tervalent manganese are in Tables 3 and 4 respectively. These indicate a bimolecular reaction between the reactants without any initial complex formation.

(c) *Oxidations of* trans-1 : 2-*dimethylcyclohexane*-1 : 2-*diol.* The first-order relation with respect to the diol (Table 5) shows that the diol does not form a complex with the manganic salt.

TABLE 3.

Initial [Mn^{III}] 0·0162M. [P_2O_7] 0·119M. pH 1·01 (glass electrode). Temp. 40°.

Diol concn. (10^{-3}M)	1·44	1·44	2·88	4·32	5·76	7·32	8·64
Initial rate (10^{-3} mole $l.^{-1}$ $hr.^{-1}$)	1·58	1·37	3·56	5·03	6·50	7·83	9·90
Rate/[Diol]	1·10	0·95	1·23	1·16	1·13	1·07	1·15

TABLE 4. (Units as in Table 3.)

Diol concn. 2·03 × 10^{-3}M. pH 0·60.

Mn^{III} concn.	2·82	5·64	8·46	11·3	14·1	16·9
Initial rate	0·89	2·00	2·6	3·3	5·0	5·8
Rate/[Mn]	0·32	0·36	0·31	0·29	0·36	0·34

Diol concn. 6·88 × 10^{-3}M. pH 1·01.

Mn^{III} concn.	6·5	8·5	9·75	13·0	13·7	16·2	17·1
Initial rate	2·9	3·8	4·8	5·9	7·5	9·1	9·9
Rate/[Mn]	0·45	0·45	0·49	0·45	0·55	0·56	0·59

TABLE 5. (Units as in Table 3.)

Initial [Mn^{III}] 0·0135M. [P_2O_7] 0·109M. pH 0·04. Temp. 40°.

Diol concn.	7·02	3·51	2·38	1·82	1·40	1·12	0·91	0·70
Initial rate	9·78	3·96	3·64	2·01	1·85	1·61	1·21	0·91
Rate/[Diol]	1·39	1·13	1·53	1·10	1·32	1·44	1·33	1·30

TABLE 6. (Units as in Table 3.)

Initial [Diol] 16·7 × 10^{-3}M. [P_2O_7] 0·119M. pH 0·20. Temp. 39·8°.

Mn^{III} concn.	3·4	6·8	10·2	10·2	13·6	16·2
Initial rate	4·8	9·0	15·3	16·7	19·9	27·8
Rate/[Mn^{III}]	1·4	1·3	1·5	1·6	1·5	1·7

Initial [Diol] 3·51 × 10^{-3}M. [P_2O_7] 0·11M. pH 0·04. Temp. 45°.

Mn^{III} concn.	2·75	4·13	5·51	6·89	8·27	9·65	13·8
Initial rate	3·66	3·70	3·71	4·38	4·32	4·43	4·80

TABLE 7. (Units as in Table 3.)

Initial $[Mn^{III}]$ $16{\cdot}2 \times 10^{-4}$M. $[P_2O_7]$ 0·12M. pH 0·19. Temp. 40°.

Diol concn.	2·66	3·33	6·65	10·0
Initial rate	3·12	4·8	10·8	13·1
Rate/[Diol]	1·2	1·4	1·6	1·3

TABLE 8. (Units as in Table 3.)

Initial [Diol] = $13{\cdot}3 \times 10^{-4}$M. $[P_2O_7]$ 0·12M. pH 0·19. Temp. 40°.

Mn^{III} concn.	3·25	6·5	9·75	13·0
Initial rate	0·36	1·5	3·2	6·3
Rate/$[Mn^{III}]^2$	0·34	0·36	0·34	0·37

At low $[Mn^{III}]$/[Diol] ratios the first-order relation is again found (Table 6), but the reaction order decreases when $[Mn^{III}]$ is present in excess. A highly speculative interpretation of this would be that the dimethyl*cyclo*hexanediol molecules have to attain a particular conformation before complete oxidation can occur.

(d) *Oxidations of* cis-cyclo*hexane*-1 : 2-*diol*. The reaction seems to be a second-order process with respect to $[Mn^{III}]$ (Table 8). This would accord with a rate-determining stage in which a complex ion Mn(diol)(pyrophosphate)$_2$ was attacked by a second molecule of manganic pyrophosphate. Reaction is of first order with respect to the diol (Table 7).

cis-1 : 2-Dimethyl*cyclo*hexane-1 : 2-diol was oxidised extremely slowly. This would be the case if the chelated complex proved to be very stable.

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181. *Mechanism of Substitution at a Saturated Carbon Atom. Part L.* Kinetic Effects of Phenyl and Halogen Substituents in Alkyl Halides on their Reactions with Halide Ions in Acetone.*

By P. B. D. DE LA MARE and E. D. HUGHES.

The effects of phenyl and halogen substituents on the rates of halogen exchange of alkyl halides in acetone have been examined by investigation of bromine or chlorine exchange, by the use of radio-isotopes of the halogens, in the compounds CH_3Cl, $Ph{\cdot}CH_2Cl$, CH_2Br, $Ph{\cdot}CH_2Br$, Ph_2CHBr, Ph_3CBr, CH_2Br_2, CBr_4. In bimolecular substitution, corresponding methyl and benzyl halides react at similar rates, though the phenyl substituent decreases the activation energy. The introduction of a second phenyl substituent reduces the rate by a factor of about 300 and the activation energy is now increased. It is concluded that the polar and steric influences of the first phenyl substituent have approximately balancing effects on rate but that the steric effect of the second phenyl group is dominant. Exchange in triphenylmethyl bromide was too rapid for measurement under our conditions, and it is likely that the unimolecular mechanism of substitution is here in control. In methylene bromide, bimolecular exchange occurred 3500 times more slowly than in methyl bromide and, under the same conditions, carbon tetrabromide underwent exchange too slowly for measurement. The measured retarding effect of the halogen substituent is attributed mainly to a polar influence, which increases the activation energy.

THIS paper records a preliminary survey of the effect of introducing phenyl and halogen substituents into alkyl groups on the rates of bimolecular halogen exchange of alkyl halides with halide ions in acetone. The reactions examined were those of chlorine exchange and bromine exchange, both by the use of radio-isotopes of the halogens.

The effects of phenyl substituents were explored in the series methyl, benzyl, benzhydryl, triphenylmethyl. Some rates of bimolecular chlorine exchange between methyl chloride

* Part XLIX, *J.*, 1955, 3200.

and lithium radio-chloride in solvent acetone were recorded in Part XLII.[1] Rate data for the corresponding reaction of benzyl chloride are given in Table 3 (Experimental section). They refer to approximately the same salt concentration as the previous measurements on methyl chloride. It is found that methyl and benzyl chloride undergo the exchange reaction at similar rates, which, however, depend on different Arrhenius parameters, as will be discussed below. In the same conditions, benzhydryl chloride undergoes the corresponding reaction somewhat too slowly for convenient measurement, and the series of alkyl bromides was therefore examined.

Some rates of bimolecular exchange of bromine between methyl bromide and lithium radio-bromide in acetone are already given in Part XLV.[2] Some rate measurements referring to the corresponding reaction of benzyl bromide are recorded in Table 3. Again it is found that the methyl and benzyl halides react at similar rates. In the same conditions, benzhydryl bromide undergoes the analogous reaction at rates which can be measured, but are about 300 times smaller than the rates for methyl or benzyl bromide. Some measurements on benzhydryl bromide are included in Table 3. These measurements were made at various salt concentrations. The second-order rate coefficients showed a negative salt effect, somewhat smaller than those encountered previously.[2] The magnitude of the effect having been determined, rates were corrected to the salt concentration which was taken as standard in the earlier work.[2] An attempt to extend the measurements to the exchange reactions of triphenylmethyl bromide was frustrated by the great rapidity of the exchange, which, below −20° in acetone, was complete before the first measurement could be made.

The rates at common temperatures, and the parameters of the Arrhenius equation, for the halogen exchanges of the successively phenyl-substituted alkyl chlorides and bromides are collected in Table 1. The figures suggest that the phenyl substituent has two effects on the rates of these bimolecular substitutions. The first is an accelerating polar effect of a type discussed several times before:[3] the phenyl substituent, facilitating bond fission by the electromeric process $Ph\overset{\curvearrowright}{—}C\overset{\curvearrowright}{—}Hal$, allows a reduced amount of bond establishment by the attacking reagent to stimulate disproportionately extensive bond-loosening, with the result that the transition state can be formed at a reduced energy of interaction. The second and third phenyl substituents should repeat this polar energetic effect, and so, if steric effects did not intervene, the energy of activation should fall with continued phenyl substitution in successive comparable decrements.

The second kinetic effect of the phenyl substituent will indeed be its steric effect. In principle, this should influence both the energy and the entropy of activation; but it will not make its first prominent appearance in these two factors of reaction rate at the same stage of successive phenyl substitution. The first phenyl group should reduce the entropy of activation, and therefore the frequency factor of reaction rate, partly by its ponderal effect,[4] and partly by stopping the interconversion of conformations; for the stereochemistry of bimolecular benzyl transition states is somewhat similar to that of 2:6-disubstituted diphenyl molecules. On the other hand, as an examination of models shows, the first phenyl substituent will have only a trifling effect on the energy of activation. Whether the second and the third phenyl substituent will further depress the entropy of activation, it is hard to say, without a more elaborate theoretical investigation than has yet been made. But the second phenyl group will certainly introduce the first large steric contribution to the energy of activation; and the third will add a much larger contribution still.

The interpretation of the observations, which follows from these principles, is that the polar energetic and the steric entropic effects of the first phenyl substituent have approximately balancing effects on the rate, but that the steric effect of the second phenyl group is much larger, and, indeed, is dominating. A possible explanation of the great

[1] de la Mare, *J.*, 1955, 3169.
[2] de la Mare, *J.*, 1955, 3180.
[3] Hughes, Ingold, and Shapiro, *J.*, 1936, 225; Hughes, *Trans. Faraday Soc.*, **1941**, **37**, 207; Vernon, *J.*, 1954, 4462; de la Mare, Fowden, Hughes, Ingold, and Mackie, *J.*, 1955, 3223, footnote.
[4] de la Mare, Fowden, Hughes, Ingold, and Mackie, *J.*, 1955, 3200.

increase of rate which follows the introduction of the third phenyl group is that the unimolecular mechanism of substitution now takes control. We have no proof of this, but it is a reasonable assumption, inasmuch as the unimolecular mechanism is subject to only small steric effects, whilst, as rate is determined by a bond fission, without any accompanying bond formation, each phenyl substituent must introduce a large factor of polar acceleration.

TABLE 1. *Rates (k_2 in sec.$^{-1}$ mole^{-1} l.) at common temperatures, and Arrhenius frequency factors (B_2 in sec.$^{-1}$ mole^{-1} l.) and activation energies (E in kcal. mole^{-1}) in isotopic exchanges of halogen between arylethyl halides and lithium halides in acetone.*

	With LiCl, 0·028M		With LiBr at or corrected to 0·024M			
	CH_3Cl	$Ph{\cdot}CH_2Cl$	CH_3Br	$Ph{\cdot}CH_2Br$	Ph_2CHBr	Ph_3CBr
10^5k_2 (0°)	0·16	0·16	1120	1120	3·3	Large
10^5k_2 (25°)	3·9	2·8	13,000	—	45	Large
$\log_{10}B_2$	10·4	8·9	10·7	—	9·2	—
E	20·2	18·3	15·8	—	17·2	—

The present inspection of the kinetic effect of halogen substituents on the bimolecular exchanges is confined to a comparison of the rate of exchange of bromine of methyl bromide, and of methylene bromide, with lithium bromide in acetone, together with qualitative observations on the behaviour of carbon tetrabromide towards this reagent. The rate data for methyl bromide are in Part XLV,[2] whilst those for methylene bromide are in Table 4 (Experimental section). It is found that methylene bromide undergoes the exchange 3500 times more slowly than methyl bromide, if we compare equal numbers of molecules, or 7000 times more slowly, if the comparison is with equal numbers of bound bromine atoms. Further, practically the whole of this kinetic effect is found in the energy factor of reaction rate. Carbon tetrabromide underwent exchange too slowly for measurement at the temperatures of the other measurements, *e.g.*, 25°; and, when the temperature was raised to 87° to obtain an appreciable, though still slow, exchange, the reaction, to judge from indications such as colour development, seemed to take a complex form. It thus appears that bimolecular nucleophilic exchange with this halide is very slow indeed.

The rates at common temperatures, and the Arrhenius frequency factors and activation energies for the exchange reactions of the bromomethanes are in Table 2. The values for methyl bromide have been corrected by means of the relation given in Part XLV,[2] to correspond to the salt concentration (0·06M) applying to this comparison.

It appears that, in the absence of any strongly electron-releasing substituent, the effect of one, or of several, halogen substituents is to retard exchange, essentially by raising the energy of activation. In methylene bromide at least, this effect is too large to be ascribed to steric hindrance; and it is accordingly to be classified as a polar effect. It may be suggested that the effect arises mainly from an increased stability conferred by the second halogen atom on the initial state of the organic molecule, perhaps by a hyperconjugative analogue of the balanced two-way electron-redistribution, which so greatly increases the stability of carbon dioxide:

TABLE 2. *Rates at common temperatures, and Arrhenius frequency factors and activation energies (units as in Table 1) in isotopic exchange of bromine between bromomethanes and lithium bromide in acetone at the common salt concentration* 0·060M.

	CH_3Br	CH_2Br_2	CBr_4
10^5k_2 (0°)	860	0·18	Small
10^5k_2 (25°)	10,000	2·9	Small *
$\log_{10}B_2$	10·6	10·7	—
E	15·8	20·9	—

* $k_2 > 10^{-6}$ l. mole^{-1} sec.$^{-1}$ at 87°.

Experimental

The organic substances were prepared or purified by standard methods, and the inorganic as described in Parts XLII and XLV.[1,2] The methods of studying the exchanges were as described in the same papers, except for the special points noted below.

The separations of organic from inorganic halide, prior to the measurements of radioactivity, in the exchange reactions of benzyl and benzhydryl bromide, and that of carbon tetrabromide, were effected by partition between benzene and water.

In the reaction of benzhydryl bromide, the formula, deduced from the results, and used for the standardisation of rates with respect to salt effects, was

$$\log_{10}\{k_2^{(b)}/k_2^{(b_0)}\} = -0{\cdot}22 \log_{10} (b/b_0)$$

The rapidity of exchange between triphenylmethyl bromide and lithium radio-bromide was shown as follows. Solutions of the reagents in acetone were cooled to −80° and mixed, then warmed just enough to secure dissolution of the separated triphenylmethyl bromide, and again cooled to −80°. The crystals of triphenylmethyl bromide were collected and shaken with

Table 3. *Second-order rate-constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of exchange between arylalkyl halides and lithium radio-halides in acetone.*

Temp.	a = [RHal]	b = [LiHal]	Counting rates C	$C - X_1$	$C - X_2$	$t_2 - t_1$ (min.)	$10^3 k_2$ [a]	Mean $10^3 k_2$ [a]
Benzyl chloride and lithium radio-chloride								
48·2°	0·1015	0·0281	876·8	880·2	765·2	77·0	30·0	
					784·5	73·5	25·0	
					788·9	68·5	26·8	27·5
25·0	0·1050	0·0290	889·8	889·8	719·4	1254	2·76	
					725·9	1163	2·86	
					673·3	1567	2·95	
					689·5	1540	2·73	2·83
18·6	0·1061	0·0293	891·5	886·7	695·6	2787	1·44	
					668·3	2840	1·65	
					693·9	2834	1·43	
					698·1	2853	1·38	1·47
Benzyl bromide and lithium radio-bromide								$10^5 k_2$[(c)=0·1]
0·0	0·0618	0·0368	1117	1116	994·2	10·6	970	
					973·4	11·5	1080	
					937·6	16·5	990	
					1010·0	10·9	810	1120
Benzhydryl bromide and lithium radio-bromide								
35·4	0·0445	0·0409	1186	1199	873·4	131·7	106·9	
					855·7	142·0	107·6	
					861·0	149·5	99·6	
					813·6	160·0	114·9	
					802·3	180·2	107·3	118·6
25·0	0·0451	0·0415	1186	1199	897·3	307·3	40·4	
					891·9	322·4	39·5	
					884·7	334·2	39·5	
					880·2	346·9	38·8	
					864·2	353·5	41·0	44·6
10·5	0·0286	0·0532	322·1	320·5	275·1	1304	8·41	
					270·1	1346	9·14	
					267·8	1386	9·46	10·7
	0·0287	0·0267	322·1	320·5	253·8	1438	10·7	
					255·3	1411	10·2	
					246·4	1617	11·0	11·1
	0·0287	0·0178	322·1	320·5	236·3	1711	11·5	
					238·3	1727	11·1	10·6
−0·1	0·0630	0·0407	1057	1065	793·9	3018	2·85	
					784·1	3042	2·95	
					805·0	3073	2·64	
					608·4	7078	2·74	
					608·2	7089	2·75	3·13

water. The neutralised solution was evaporated, and the sodium bromide in the residue was taken up in water. The filtrate from the triphenylmethyl bromide was evaporated, and the residue was extracted with benzene and then dissolved in water. The two solutions of saline bromide, thus obtained, were shown to have the same specific activity to within the experimental error of a few units per cent.

In the reaction of methylene bromide the separation of organic from inorganic bromide was effected by the evaporation method. For the calculations of rate constants a slight modification of the usual formula was required, *viz.* :

$$k_2 = \frac{2 \times 2{\cdot}303}{(2a + b)(t_2 - t_1)} \log_{10}\left\{\left[1 - \frac{X_1}{C}\left(1 + \frac{b}{2a}\right)\right]\left[1 - \frac{X_2}{C}\left(1 + \frac{b}{2a}\right)\right]^{-1}\right\}$$

The details of some kinetic runs are recorded in Tables 3 and 4. The headings of the Tables are explained in Part XLII.[1] Excepting the cases mentioned above, the rate coefficients at specific ionic strength (*e.g.*, $k_2^{0\cdot024}$) were obtained by the procedure previously described.[2]

TABLE 4. *Second-order rate-constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of halogen exchange between methylene dibromide and lithium radio-bromide in acetone.*

Temp.	a = $[CH_2Br_2]$	b = [LiBr]	Counting rates C	$C - X_1$	$C - X_2$	$t_2 - t_1$ (min.)	$10^5 k_2$ [a]	Mean $10^5 k_2^{(0\cdot040)}$
44·6°	0·0911	0·0571	1254	1238	1058	70·2	19·8	
					1007	82·0	22·4	
					979·0	93·0	22·5	
					954·6	102·0	22·8	
					928·8	120·0	21·4	
					921·2	120·0	22·0	21·3
25·0	0·1968	0·0588	1802	1820	1188	1354	2·74	
					1175	1379	2·73	
					1153	1415	2·82	
					1177	1416	2·68	
					1144	1492	2·72	2·72
−0·1	0·0239	0·0610	398·8	413·6	327·1	18,910	0·096	
					318·4	18,914	0·107	
					327·6	18,924	0·096	
					330·6	18,894	0·091	
					323·4	19,964	0·095	
					323·8	19,954	0·094	0·097

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182. *Mechanism of Substitution at a Saturated Carbon Atom. Part LI.* ortho-Effects in Solvolysis of Arylalkyl Halides, illustrating Steric Retardation in a Unimolecular Substitution.*

By J. C. Charlton and E. D. Hughes.

This paper records rates of solvolysis of (i) benzyl chloride and methyl-substituted benzyl chlorides in 50% aqueous ethyl alcohol at 35° and (ii) 1-phenylethyl chloride and its methyl-substituted derivatives in ethyl alcohol at several temperatures. For the chlorides of the benzyl series, *o*- and *p*-methyl substituents cause comparable acceleration and it is concluded that practically pure polar influences are operative. In 1-phenylethyl chlorides, while the introduction of *p*-methyl and of one *o*-methyl substituent exerts similar facilitating effects, a second *o*-methyl group has much less influence. It is concluded that with two *o*-methyl groups present we have, superimposed on a general accelerating influence of a polar nature, a retarding steric effect. This is attributed to the development of a steric pressure (resulting in an increase of activation energy of *ca.* 1·0—1·5 kcal./mole) between α- and *o*-methyl substituents in the transition state of ionisation.

The existence of a pattern in the incidence of steric hindrance among reactions was first indicated in 1941, when it was noted that unimolecular mechanisms should be generally insensitive, and bimolecular mechanisms generally sensitive, to steric hindrance.[1]

This difference between unimolecular and bimolecular mechanisms represents a broad distinction. It does not mean either that steric conditions have no effect at all on the rate of any unimolecular reaction, or that all bimolecular reactions are similarly sensitive to steric hindrance. In each of the main parts of the pattern there is a light and shade of steric effects. The present papers are concerned with the closer description of some of this detail, within the limited field of nucleophilic substitution, and this particular paper deals with one of the details relating to the unimolecular mechanism of substitution.

We can think of two general reasons why steric conditions might have somewhat mild kinetic effects of either sign on unimolecular nucleophilic substitutions. First, in the formation of the unimolecular transition state, a bond has to be stretched. Now, although normal molecules do not sustain internal pressures nearly as large as those which can be built up in bimolecular transition states, many normal molecules probably do sustain appreciable internal pressures, which might to some extent be relieved by the stretching of a bond.[2] Thus an activation energy would be reduced, and a steric acceleration of the reaction would be observed. The second possibility is that the whole geometry of the atomic system around the reaction centre might be so changed, on the formation of the transition state, that some completely new pressures would be developed. If such new pressures should more than outweigh any relief of pressure due to the bond-stretching, we should observe a (probably mild) steric retardation of a unimolecular substitution.

Several possible examples of steric acceleration in unimolecular nucleophilic substitution have been suggested. This type of explanation was tentatively applied to the solvolysis of highly branched *tert.*-alkyl halides, RCl ⟶ ROH, ROEt, etc., in order to account for the considerable acceleration which follows upon the complete γ-methylation of *tert.*-butyl chloride $(H_3C)_3CCl$, to give tri-*tert.*-butylmethyl chloride $(Me_3C)_3CCl$.[3] It was similarly applied to the solvolysis of diazonium ions, ArN_2^+ ⟶ ArOH, etc., in order to interpret the acceleration which follows the introduction of methyl and phenyl substituents into an *ortho*-position in the aryldiazonium ion, though polar factors so operate that the introduction of the same groups into the *para*-position retards this reaction.[4]

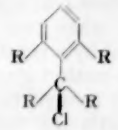
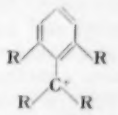
* Part L, preceding paper.

[1] Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603; Day and Ingold, *ibid.*, p. 686.
[2] H. C. Brown, *Science*, 1946, **103**, 385, and later papers.
[3] F. Brown, Davies, Dostrovsky, Evans, and Hughes, *Nature*, 1951, **167**, 987; Hughes, *Bull. Soc. chim. France*, 1951, **18**, C47; Bartlett, *ibid.*, p. C108; *J. Amer. Chem. Soc.*, 1955, **77**, 2801.
[4] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell, London, 1953, p. 801.

We now record an attempt to realise steric retardation in a unimolecular nucleophilic substitution by arranging for a suitable geometrical change in the transition state.

For this purpose, we go over to the series of simple and substituted benzyl halides, most of which undergo unimolecular solvolysis in easily realised conditions; and we examine the kinetic effect of any interaction there may be between α-substituents and *ortho*-substituents, using also *para*-substituents as a control on such polar effects as may be exerted by the *ortho*-substituents employed.

The geometrical situation is as follows. In a benzyl-type halide, the bonding in the side chain is tetrahedral; and so neither of the two α-groups need be, and in general neither will be, in the plane of the ring and its *ortho*-substituents (see I). In the carbonium ion, however, the side-chain bonding is trigonal, and, on account of conjugation, is coplanar with the aromatic ring, so that both α-groups and both *ortho*-groups necessarily come into the same plane (see II). It follows that, if, in the original molecule, α-groups are not much further off from *ortho*-groups than the distances at which steric compression would begin, then, in the carbonium ion, appreciable steric pressures might be developed; and that if steric pressure between α-groups and *ortho*-groups is incipient in the original molecule, then it will certainly become considerable in the carbonium ion.

(I)  (II) 

The transition state of the rate-controlling ionisation is in an intermediate stereochemical situation: the side-chain will not be fully co-planar with the ring; but the bonds holding the α-groups will have moved in that direction; and therefore, if steric compression was incipient in the original molecule, it could become appreciable in the transition state. This would lead to an increased energy of activation, and thus to a steric retardation of the reaction.

This investigation is restricted to the effect of methyl substituents. We may describe, first, the results obtained in the series that provides our standard of reference, a series in which steric effects are absent, so that we isolate kinetic behaviour under the polar effects of the methyl substituents. This is the series of benzyl halides having two α-hydrogen atoms (*i.e.*, no methyl group) in the side chain, and up to three methyl groups in *ortho*- and *para*-positions in the ring. Measurement of models shows that steric compression between α-hydrogen and *ortho*-groups is inappreciable or scarcely appreciable, not only in the original molecule, but also in the fully formed carbonium ion, and therefore also in the transition state of ionisation. In this series, no substantial steric effects can influence unimolecular substitution.

The reaction studied was the solvolysis of the benzyl chlorides in 50% aqueous ethyl alcohol, one of the more favourable solvents for unimolecular reactions. The reactions were followed by measuring the production of either chloride ion or hydrogen ion. Some first-order rate constants at 35°, and corresponding relative rates are collected in Table 1.

TABLE 1. *First-order rate-constants* (k_1 *in sec.*$^{-1}$) *of solvolysis of benzyl chloride and of methyl-substituted benzyl chlorides in* 50% *aqueous ethyl alcohol at* 35·0°.

	10^5k_1			
Benzyl chloride	By Cl^-	By H^+	Relative rates	
Parent	0·243, 0·236	—	1	—
2-Me	1·26, 1·25	—	5·2	—
2 : 6-Me_2	6·87	6·82	29 = 5·2 × 5·6	—
4-Me	2·32, 2·31	—	9·6	1
2 : 4-Me_2	20·7, 20·5	20·0	85	8·8
2 : 4 : 6-Me_3	—	313, 312	1300	135 = 8·8 × 15·3

It will be seen that *o*- and *p*-methyl substitutents exert comparable accelerating effects, and that, in particular, the second *ortho*-group introduces a factor of acceleration which

is of the same order of magnitude as that given by the first. This must be a practically pure polar effect. Steric hindrance is characterised by the suddenness of its build-up after the first onset; and, if the first *ortho*-group were introducing an appreciable steric retarding factor, then the second would introduce a much larger one, and the rates would not show the relations they do. Equally, the accelerations are too nearly uniform to be regarded as steric accelerations. All this is consistent with the models of the molecules and transition state, which tell us to expect no steric effect of any kind.

The general consistency of the data supports the view that the unimolecular mechanism is the main reaction route. It will undoubtedly be the sole mechanism in most cases, and particularly in those in which we are concerned to show the absence of steric effects by pairs of *o*-methyl groups. In the example of 2 : 4 : 6-trimethylbenzyl chloride, Brown and Hudson [5] showed that solvolysis followed the unimolecular mechanism exclusively in a less ionising solvent than ours.

Against this background, we describe a study of the series of similarly methyl-substituted 1-phenylethyl chlorides. Here we have always one α-methyl group. Models show that steric compression between α-methyl and *o*-hydrogen is insignificant, not only in the original molecule, but also in the fully formed carbonium ion, and therefore also in the intermediate transition state. However, models also show that significant compressions can arise between α-methyl and *o*-methyl, though only when two *o*-methyl groups are present, since, with one alone, compression can be relieved by a rotation of the side chain. Such compression between α-methyl and one of two *o*-methyl groups is incipient, but relatively small, in the original molecule; but it is large enough to raise the energy by some kcal./mole in the carbonium ion; and therefore, although the compression will be smaller than this in the transition state, it may well be large enough to raise the energy appreciably, and hence to lead to a significant steric retardation. Of course, such a steric effect will appear in superposition upon the nearly uniform, polar, accelerative effect of *o*- and *p*-methyl groups, already illustrated in the benzyl series. But still the steric effect may be detectable, because it should not be uniform, but should be distinguished by its sudden appearance on the introduction of a second *o*-methyl group.

The process examined was the solvolysis of the 1-phenylethyl chlorides in dry ethyl alcohol, a solvent which, for this series of halides is ionising enough fully to establish the unimolecular mechanism. Actually, the rates of these reactions have been measured over ranges of temperature, but we shall first compare them at a common temperature, in the same simple way as for the benzyl series. The reactions were followed by determination of the chloride ion produced. The rates at 34·8°, and corresponding relative rates, are given in Table 2.

TABLE 2. *First-order rate-constants* (k_1 *in sec.*$^{-1}$) *of solvolysis of* 1-*phenylethyl chloride and of methyl-substituted* 1-*phenylethyl chlorides in dry ethyl alcohol at* 34·8°.

1-Phenylethyl chloride	10^5k_1	Relative rates	
Parent	0·0782	1	—
2-Me	1·26	16	—
2 : 6-Me_2	2·35	30 = 16 × 1·9	—
4-Me	3·10	40	1
2 : 4-Me_2	43·5	560	14
2 : 4 : 6-Me_3	112	1440	38 = 14 × 2·7

We notice that, in this series, the polar effects of the nuclear methyl groups are slightly larger than in the benzyl series, each methyl group (apart from a second *o*-methyl group) raising the rate by a factor of 15—40. However, second *o*-methyl groups, instead of increasing the rate by factors of at least as much, raise it by factors of 2—3 only. Evidently a retarding effect has entered here; and the manner of its entry is as expected for the steric retardation due to the flattened structure of the unimolecular transition state.

There can be no doubt that these effects do indeed apply to the unimolecular mechanism. For 1-phenylethyl chloride itself this is clear from previous work; and for representative

[5] D. A. Brown and Hudson, *J.*, 1953, 3360.

derivatives, *viz.*, the 2-methyl, 2 : 4-dimethyl, and 2 : 4 : 6-trimethyl compounds, we have verified that the rate of alcoholysis is scarcely, if at all, sensitive to added lithium ethoxide up to concentrations about 0·05M.

We should expect the polar effect of the methyl substituent to be exerted mainly on the energy factor of reaction rate, and the steric effect considered above is again an effect on energy. We have therefore measured the solvolysis rates over a temperature range with the results contained in Table 3.

TABLE 3. *First-order rate-constants* (10^5k_1 *with* k_1 *in sec.*$^{-1}$) *of solvolysis of* 1-*phenylethyl chloride and its methyl derivatives in dry ethyl alcohol at various temperatures.*

Temp.	Parent	2-Me	2 : 6-Me_2	4-Me	2 : 4-Me_2	2 : 4 : 6-Me_3
−10·0°	—	—	—	—	—	0·311
0·0	—	—	—	—	0·583	1·47
+11·6	—	—	—	—	2·83	—
14·3	—	—	—	—	—	10·8
24·9	—	0·403	0·747	0·913	14·8	36·5
34·8	0·0782	1·26	2·35	3·10	43·5	112
45·1	0·278	3·86	7·48	10·1	—	—
55·1	0·844	—	21·7	30·1	—	—
63·6	2·09	25·5	51·1	72·2	—	—
75·7	6·75	—	—	—	—	—
76·7	7·35	—	—	—	—	—
84·1	13·9	—	—	—	—	—

The Arrhenius parameters which follow from these figures are in Table 4. We see that, whereas the first *o*-methyl substituent substantially reduces the activation energy, the second does not. We assume that the similar reduction, which its polar effect would produce, is approximately cancelled by the appearance at this point of steric energy. The amount of steric energy seems to be about 1·0—1·5 kcal./mole; and, although we have not enough data to permit a theoretical treatment of the problem, such a value may be taken to imply that, in the transition state of ionisation, the system of bonds which the carbonium ion is going to retain is very considerably flattened (cf. the following paper).

TABLE 4. *Arrhenius energies of activation* (*E in kcal./mole*) *and frequency factors* (*B in sec.*$^{-1}$) *for the solvolysis of* 1-*phenylethyl chloride and its methyl derivatives in dry ethyl alcohol.*

	E	$\log_{10} B$		*E*	$\log_{10} B$
Parent	22·8	10·2	4-Me	22·2	11·3
2-Me	21·5	10·4	2 : 4-Me_2	20·7	11·4
2 : 6-Me_2	21·6	10·8	2 : 4 : 6-Me_3	20·6	11·7

EXPERIMENTAL

Preparations.—The benzyl chloride, twice distilled, had b. p. 66°/13·5 mm., n_D^{25} 1·5360. *p*-Toluic acid was reduced with lithium aluminium hydride in ether to 4-methylbenzyl alcohol, m. p. 59°, which was converted, by treatment with thionyl chloride in benzene, into 4-methylbenzyl chloride: the latter after non-ebullient distillation at a low pressure, and fractional freezing, had m. p. 5·2°, n_D^{25} 1·5320, and the theoretical content of hydrolysable chlorine. *o*-Toluic acid was similarly converted into 2-methylbenzyl alcohol, m. p. 35·5—36°, and thence into 2-methylbenzyl chloride, m. p. 4·8°, n_D^{25} 1·5400.

2 : 4-Dimethylbenzyl chloride, prepared directly from *m*-xylene, formaldehyde, and hydrogen chloride as described by Nauta and Dienska,[6] had b. p. 108—109°/20 mm., n_D^{25} 1·5372, and the correct chloride content. Its identity was checked by hydrolysis in aqueous acetone to the alcohol, m. p. 28—29° (Found: C, 79·3; H, 8·4. Calc. for $C_9H_{12}O$: C, 79·4; H, 8·9%) (Hinrichsen [7] gives m. p. 22°), and oxidation of the latter with permanganate to 2 : 4-dimethylbenzoic acid, m. p. 124° (Found: C, 71·8; H, 6·8. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·7%) (Stephen, Short, and Gladding [8] give m. p. 125°). 2 : 6-Dimethylbenzoic acid, m. p. 116°, prepared from 2-bromo-*m*-xylene (from *m*-2-xylidine) by the Grignard method with carbon dioxide, was reduced with lithium aluminium hydride to 2 : 6-*dimethylbenzyl alcohol* (48%

[6] Nauta and Dienska, *Rec. Trav. chim.*, 1936, **55**, 1000.
[7] Hinrichsen, *Ber.*, 1888, **21**, 3085.
[8] Stephen, Short, and Gladding, *J.*, 1920, **117**, 522.

yield), which, when crystallised from light petroleum, had m. p. 83·5° (Found : C, 79·8; H, 9·0. $C_9H_{12}O$ requires C, 79·4; H, 8·9%), and, on treatment with thionyl chloride in benzene, gave **2 : 6-*dimethylbenzyl chloride***, m. p. 34° (Found : C, 69·7; H, 7·3; Cl, 23·0. $C_9H_{11}Cl$ requires C, 69·9; H, 7·2; Cl, 22·9%). **2 : 4 : 6-Trimethylbenzyl chloride**, prepared from mesitylene by Nauta and Dienska's method,[8] had m. p. 45—46°. Its identity was checked by hydrolysis with aqueous acetone to **2 : 4 : 6-trimethylbenzyl alcohol**, m. p. 88° (Found : C, 80·4; H, 9·7. Calc. for $C_{10}H_{14}O$: C, 80·0; H, 9·4%) (Carré [9] gives m. p. 88—89°).

1-Phenylethyl alcohol, purified by way of its hydrogen phthalate,[10] had b. p. 106—107°/22—23 mm., n_D^{25} 1·5254, and on treatment with thionyl chloride in benzene, gave **1-phenylethyl chloride** having b. p. 80—81°/19 mm., n_D^{25} 1·5252, and the theoretical content of hydrolysable chlorine. **1-*p*-Tolylethyl alcohol**, prepared from *p*-bromotoluene and acetaldehyde by the Grignard method, had b. p. 108—110°/12 mm., n_D^{25} 1·5221, and with thionyl chloride in benzene gave **1-*p*-tolylethyl chloride**, which was purified by non-ebullient distillation. **1-*o*-Tolylethyl alcohol**, similarly prepared, had b. p. 119°/21 mm., n_D^{25} 1·5292, and gave **1-*o*-tolylethyl chloride**, b. p. 99·5°/19 mm., n_D^{25} 1·5318.

2 : 4-Dimethylacetophenone [11] had b. p. 109°/14 mm., n_D^{25} 1·5319, and gave a **2 : 4-*dinitrophenylhydrazone***, m. p. 170° (Found : C, 58·0; H, 4·8; N, 16·5. $C_{16}H_{16}O_4N_4$ requires C, 58·5; H, 4·9; N, 17·1%). The ketone was reduced with lithium aluminium hydride in quantitative yield to **1-(2 : 4-dimethylphenyl)ethyl alcohol**, b. p. 125—126°/16—17 mm., n_D^{25} 1·5245. This was converted with thionyl chloride into **1-(2 : 4-dimethylphenyl)ethyl chloride**, which was purified by non-ebullient distillation, had a correct chlorine content, and was characterised by conversion into **1-[1-(2 : 4-dimethylphenyl)ethyl]pyridinium chloride**, m. p. 153° (Klarges and Keil [12] give m. p. 153°). **1-(2 : 6-*Dimethylphenyl*)*ethyl alcohol*** prepared by the Grignard method from 2-bromo-*m*-xylene and acetaldehyde, had m. p. 69° after crystallisation from light petroleum (Found : C, 80·6; H, 9·5. $C_{10}H_{14}O$ requires C, 80·0; H, 9·4%), and, on treatment with thionyl chloride as usual, gave **1-(2 : 6-*dimethylphenyl*)*ethyl chloride***, which was purified by non-ebullient distillation (Found : Cl, 20·8. $C_{10}H_{13}Cl$ requires Cl, 21·1%). **2 : 4 : 6-Trimethylacetophenone** was prepared from mesitylene, and converted into **1-mesitylethyl alcohol**, and **1-mesitylethyl chloride**, as described by Charlton and Hughes.[13]

Kinetics.—For the chlorides of the 1-phenylethyl series the sealed-tube method was used. The tubes were charged with the aid of an automatic pipette, jacketed at 0° when necessary. With chlorides of the benzyl series, the halide was contained in a flask in a thermostat and, from a pipette jacketed at the same temperature, a volume of dry ethyl alcohol was first added and then, with efficient stirring throughout, an equal volume of water. In this way homogeneity and temperature control were quickly attained and aliquot portions of the reaction mixture were withdrawn at suitable intervals and analysed. The progress of reaction was determined by measurement of either acid or chloride ion in work with benzyl chlorides, and by the latter method only in work with 1-phenylethyl chlorides. For acid determination the samples were added to cooled acetone, and the resulting solutions were titrated with 0·1N-sodium hydroxide, with lacmoid as indicator. For the chloride-ion measurements, the tube contents or aliquots were partitioned between carbon tetrachloride and water, and the aqueous solution was titrated electrometrically with 0·01N-silver nitrate.

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[9] Carré, *Compt. rend.*, 1910, **151**, 150.
[10] Houssa and Kenyon, *J.*, 1930, 2260.
[11] Perkin and Stone, *J.*, 1925, **127**, 2283.
[12] Klarges and Keil, *Ber.*, 1903, **36**, 1637.
[13] Charlton and Hughes, *J.*, 1954, 2939.

183. *Mechanism of Substitution at a Saturated Carbon Atom. Part LII.* Polar and Steric* ortho-*Effects in Bimolecular Finkelstein Substitutions of Arylalkyl Halides.*

By J. C. Charlton and E. D. Hughes.

This paper records rates of bimolecular replacement of chlorine by iodine in (i) benzyl chloride and methyl-substituted benzyl chlorides in acetone at 0°, and (ii) 1-phenylethyl chloride and methyl-substituted derivatives in acetone at 44·5°. In series (i), *o*- and *p*-methyl substituents accelerate the reactions. It is concluded that transmitted polar factors are here involved and that direct effects also contribute to the particularly large rate increases which are observed for *o*-methyl groups. For 1-phenylethyl chlorides, a *p*-methyl group and one *o*-methyl substituent exert effects which may be ascribed similarly to polar influences. However, the second *o*-methyl group retards reaction and this is explained by assuming the incursion of a steric retardation, since on theoretical grounds steric pressure may be expected to appear in just these structural circumstances. The magnitude of the steric effect is discussed in relation to that exhibited in solvolysis (preceding paper).

Although all bimolecular reactions are in principle subject to steric hindrance, large differences of sensitivity are found between one type of reaction and another, and, even for one general reaction, between systems distinguished by the changes of geometrical relation that attend the formation of the transition state. Thus the generally greater sensitivity of bimolecular nucleophilic substitution than of bimolecular elimination to steric hindrance has been attributed to the less accessible situation of the attacked carbon of the former reaction than of the attacked hydrogen of the latter. And among bimolecular substitutions, the much more noticeable steric effects in those of alkyl than in those of aryl compounds have been explained on the basis that in the latter the molecule is planar and the attack is lateral to the plane.

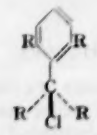
In this paper we deal with bimolecular substitutions of a third geometrical type, those of arylalkyl compounds, such as benzyl and 1-phenylethyl halides. We shall find that steric hindrance here exerts a relatively mild effect, essentially for the reason that the reacting atoms, those which undergo the greatest movements, are not themselves subject to substantial steric pressures: such pressures arise among the other parts of the arylalkyl group, because the mechanism demands a Walden inversion, and therefore certain atoms have to be moved across the aromatic plane, which may already be somewhat fully occupied.

As in the previous paper, we examine the interaction between α-methyl and *o*-methyl substituents in benzyl-type chlorides, employing also *p*-methyl substituents as a control on polar effects. The reaction now studied is the Finkelstein displacement of the chlorine as chloride ion by entering iodide ion in solvent acetone, a medium in which these nucleophilic substitutions are shown by their kinetics to be bimolecular processes.

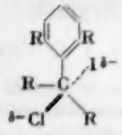
The geometrical situation is somewhat similar to that which arises in unimolecular substitutions in benzyl-type halides, but with the difference that, when the tetrahedral side-chain of the initial molecule (I) goes into the bipyramidal configuration of the transition state (II), the three preserved bonds of the α-carbon atom are bent, not merely towards the aromatic plane, as in the transition state of unimolecular substitution, but completely into a plane which will be closely assimilated to the aromatic plane. Therefore, as far as these three bonds are concerned, the geometrical conditions in the bimolecular transition state will be like those in the fully formed carbonium ion of unimolecular substitution, as discussed in the preceding paper. As in that case, steric pressure between α-hydrogen and *o*-methyl, and also between α-methyl and *o*-hydrogen, is insignificant, but steric pressure between α-methyl and *o*-methyl is considerable; although it is inescapable, and therefore effective, only when *two* *o*-methyl groups are present. In short, steric

* Part LI, preceding paper.

retardation in the bimolecular substitutions of these halides should arise in just the structural circumstances in which it does in their unimolecular substitutions; but in bimolecular substitutions the steric retardations should be stronger than in unimolecular.



(I)



(II)

Rate-constants for the reactions of ring-methylated benzyl chlorides with potassium iodide in acetone at 0° are given in Table 1. Two reagent concentrations were employed, the higher, where possible, because the disturbance from reversibility is thus reduced, the back-reaction being restricted by the precipitation of potassium chloride, and the lower inasmuch as the large rates of some of the reactions made this necessary. The general consistency of the second-order rate-constants shows that bimolecular substitutions are under observation.

TABLE 1. *Second-order rate-constants (k_2 in sec.$^{-1}$ mole^{-1} l.) for reactions of benzyl chlorides with potassium iodide in acetone at 0°.*

Rates (*a*) with [RCl] = 0·1 and [KI] = 0·02M initially.
" (*b*) " " = 0·2 " " = 0·04M "

Benzyl chloride	10^5k_2 (*a*)	10^5k_2 (*b*)	Relative rates [Column (*a*)]	
Parent	3·3	3·35	1	—
2-Me	36·8	40·5	11·2	—
2 : 6-Me_2	600	—	182 = 11·2 × 16·2	—
4-Me	5·1	5·46	1·55	1
2 : 4-Me_2	134	152	40·6	26
2 : 4 : 6-Me_3	950	—	288	186 = 26 × 7·1

An unexpected feature of these results is that, although the accelerating effect of a *p*-methyl substituent, which must be purely a transmitted polar effect, is quite small, as we should expect for a bimolecular reaction, that of an *o*-methyl substituent, even a single one, the kinetic effect of which could not possibly be steric, is considerably larger. Though it would be difficult to give a very close analysis of the figures, we assume the presence of some kind of direct polar effect of *o*-methyl groups, plausibly one deriving from an electrostatic attraction between methyl hydrogen and the semi-ionic halogen atoms in the transition state. The rate figures show no evidence of the incursion of a steric effect on the introduction of the second *o*-methyl group, and this is consistent with theoretical expectation.

The corresponding reactions of the 1-phenylethyl chlorides are slower than those of the benzyl chlorides. This is in contrast to solvolysis (preceding paper); but is to be expected if the Finkelstein substitution in acetone is bimolecular in both series of halides. In the series of 1-phenylethyl chlorides, the reaction with sodium iodide in acetone at 35—45° was shown to follow second-order kinetics by changing the initial concentrations of the reactants. The point was gone into particularly carefully in the example of 1-mesitylethyl chloride, which has been shown to undergo unimolecular racemisation in acetone (Part XLI [1]) and would therefore appear to be the case in which a unimolecular Finkelstein substitution is most probable. However, even here the reaction with sodium iodide follows second-order kinetics very approximately, the absolute rate of substitution with 0·1M-salt being of the order of 20 times greater than the unimolecular rate as given by the rate of racemisation in the presence of a similar concentration of a non-substituting salt, such as lithium perchlorate. We conclude that, with sufficient accuracy for the intended comparisons, all these substitutions are bimolecular. Some second-order rate-constants are given in Table 2.

[1] Charlton and Hughes, *J.*, 1954, 2939.

TABLE 2. *Second-order rate-constants (k_2 in sec.$^{-1}$ mole^{-1} l.) for reactions of 1-phenylethyl chloride with sodium iodide in acetone at 44·5°.*

Initially, [RCl] = 0·05, [NaI] = 0·1M, throughout.

1-Phenylethyl chloride	10^5k_2	Relative rates	
Parent	2·49	1	—
2-Me	80·4	32·3	—
2 : 6-Me_2	27·5	11·0 = 32·3 × 0·34	—
4-Me	6·07	2·44	1
2 : 4-Me_2	249	100	41
2 : 4 : 6-Me_3	173	69·5	28·5 = 41 × 0·69

As before, we find that a *p*-methyl substituent exerts a small accelerating effect, which we explain as a transmitted polar influence. Again, the first *o*-methyl substituent produces a considerably stronger acceleration, and again we assume a transmitted polar effect, supplemented by a direct polar effect, probably one of electrostatic attraction between *o*-methyl-hydrogen and transition-state halogen. Evidently we cannot account for these rates by assuming any form of steric acceleration, because such an effect would be greatly enhanced on the introduction of the second *o*-methyl group. On the contrary, the second *o*-methyl group retards the reaction; and this we explain by assuming the incursion of a steric retardation, since on theoretical grounds we expect steric retardation to appear in just these structural circumstances.

This steric retardation must be considerable, since it more than outweighs the total polar effect of an *o*-methyl group. As a rough estimate, we may assume that the steric effect alone would reduce rate by a factor in the range 50—100, or, otherwise expressed, would raise the free energy of activation by 2—3 kcal./mole, and probably the energy of activation by a very similar amount.

We may compare these estimates for our bimolecular substitution with corresponding estimates for the unimolecular substitution discussed in the preceding paper. From Table 2 of that paper it appears that, in the unimolecular process, the steric effect of the second *o*-methyl group, if it were acting alone, would diminish the reaction rate by a factor in the range 5—10, or, in other terms, would increase the free energy of activation by 1·0—1·5 kcal./mole. It was estimated from the Arrhenius parameters that the steric factor added 1·0—1·5 kcal./mole to the energy of activation. It is consistent that in the bimolecular substitution the estimated steric effects are larger, but the interesting point is that the involved energies are only about twice as large. From this it is apparent that the flattening of bonds in the transition state of ionisation must be considerable, a conclusion of importance in relation to Bartlett's discovery that the formation of those carbonium ions which cannot be flattened is resisted by very high energy barriers.[2]

We have not attempted a calculation of the compression energy in the bimolecular transition state, because it resides largely in hydrogen–hydrogen compressions. Hitherto we have not undertaken the calculation of these, because the uncertainties arising from the imperfectly known shapes of the van der Waals surfaces of the combined hydrogen atom are proportionately greater than those which affect other calculated atom-pair energies. However, a completely stiff model of the transition state, in which α- and *o*-methyl groups are accurately centred in the aromatic plane, involves two hydrogen–hydrogen compressions, each of about 1·0 Å; and it seems entirely reasonable that these could entail an amount of energy which becomes reduced by slight adjustments in the model to the estimated compression energy of 2—3 kcal./mole.

EXPERIMENTAL

Preparations.—These are described in the preceding paper.

Kinetics.—Except for the higher concentrations of potassium iodide, the sealed-tube method was employed. The tubes were charged, with separately prepared solutions of the reactants, each in the solvent (acetone, dried finally with magnesium perchlorate), with the aid of jacketted automatic pipettes, and were preserved at −80°,* until they were put into the thermostat, with

* For very fast reactions, the tubes were cooled before the introduction of the solution of the second reactant.

[2] Bartlett and Knox, *J. Amer. Chem. Soc.*, 1939, **61**, 3184; Bartlett and Lewis, *ibid.*, 1950, **72**, 1005.

shaking in order to speed the attainment of the reaction temperature. When the higher concentration of potassium iodide was desired, a thin-walled glass tube containing the organic halide was broken in a flask containing a solution of the salt at thermostat temperature, and aliquot portions of the reaction mixture were analysed at suitable intervals. The progress of reaction was followed by the determination of either iodide ion or chloride ion.

For the determination of iodide ion, the samples were partitioned between carbon tetrachloride and water, and the colourless aqueous extract was strongly acidified with sulphuric acid and titrated with ceric sulphate, the indicator being the *o*-phenanthroline–ferrous complex.

For the determination of chloride ion, it was necessary first to pump off the acetone rapidly, and then to partition the residue between carbon tetrachloride and water as quickly as possible. The iodide ion in the aqueous extract was next oxidised with sodium nitrite and sulphuric acid to iodine, which was extracted with carbon tetrachloride. The colourless aqueous solution was finally mixed with an equal volume of ethyl alcohol, and the chloride ion contained in it was titrated electrometrically with silver nitrate.

The iodide-ion method was usually employed on account of its greater simplicity; but it gave poor results for the reaction of 1-mesitylethyl chloride, probably because of an appreciable amount of hydrolysis of 1-mesitylethyl iodide during the analytical procedure. However, the chloride-ion method was applied in this case without difficulty.

Each of the rate-constants given in Tables 1 and 2 is the mean of either two or three consistent measurements.

We are indebted to Professor C. K. Ingold, F.R.S., for his interest and help in the work presented here and in the two preceding papers.

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184. *The Electronic Spectrum of Formaldehyde.*

By J. C. D. Brand.

The banded ultraviolet spectrum of formaldehyde (2500—5500 Å) is characterised as an electronic transition to a singlet $^{e}A''$ excited state. The stereochemical configuration of the upper state is non-planar, but the plane bisecting the H–C–H bond angle is a symmetry plane of the nuclei (point-group C_s) and the excited electronic wave-function is antisymmetric to this plane. The transition is allowed by the selection rules if the dipole moment change is parallel to the *b*-axis of inertia; and the low intensity is attributed partly to the change of nuclear configuration (Franck–Condon principle) and partly to the intrinsically small overlap of the electronic wave functions.

The rotational constants $A_{[v]}$ and $D_{[v]} = (B_{[v]} + C_{[v]})/2$ of the vibrationless level of the A'' state are evaluated from the resolved rotational structure of the fluorescence bands. The values are consistent with the following set of geometrical parameters: C–H = 1·09$_1$ Å (assumed), C–O = 1·32$_2$ Å, $\widehat{HCH} = 120°$, and $\widehat{HCO} = 116\frac{1}{2}°$. The hybridisation at the central carbon atom (between sp^2 and sp^3) is not well defined, and possible reasons for this are discussed.

The electronic band spectrum of formaldehyde has been discussed in many papers. The absorption bands, extending from 2300 to about 3530 Å,[1,2] were first recorded by Henri and Schou, and a brilliant analysis of the rotational structure was later completed by Dieke and Kistiakowsky.[3] The vibrational analysis has been developed more slowly, but absorption intervals of 1180 and 824 cm.$^{-1}$ were noted in the early work and the assignment of the former to the C–O stretching frequency of the excited state[4] has been confirmed by measurements with isotopic formaldehyde.[5] The fluorescence spectrum,

[1] (*a*) Henri and Schou, *Z. Physik*, 1928, **49**, 774; (*b*) Schou, *J. Chim. phys.*, 1928, **25**, 665; 1929, **26**, 1.
[2] Everett and Minkoff, *Trans. Faraday Soc.*, 1948, **44**, 816.
[3] Dieke and Kistiakowsky, *Phys. Rev.*, 1934, **45**, 4.
[4] Herzberg, *Trans. Faraday Soc.*, 1931, **27**, 378.
[5] Sponer and Teller, *Rev. Mod. Physics*, 1941, **13**, 75.

first observed as a chemiluminescence,[6] is readily excited either optically [7] or in a discharge,[8] progressions in the ground state carbonyl frequency being strongly marked. As there is outwardly very little resemblance in the structure of the fluorescence and the absorption spectra, it has frequently been argued that different electronic levels (or levels of different multiplicity) are involved,[8b] and attempts to interpret the spectrum in terms of a single electronic transition and a *planar* excited state have always run into serious difficulty.[9] The assumption of a *pyramidal* excited state, however, offers a promising solution of several outstanding problems in the analysis:[10] this hypothesis is adopted in the present paper, and all the important transitions and resolved rotational structure are interpreted, new experimental results for [$^2H_1$]- and [$^2H_2$]-formaldehyde being used. A brief account of these experiments has already been published.[11]

Experimental

[$^2H_2$]Formaldehyde was prepared by photosensitised combination of deuterium and carbon monoxide.[12] [$^2H_1$]Formaldehyde (mixed with the [$^1H_2$]- and the [$^2H_2$]-isomer) was obtained similarly, a mixture of hydrogen and deuterium being used.

Spectra.—Spectra were recorded in absorption with a Hilger E 2 quartz spectrograph, and in emission with a medium glass spectrograph (9 Å/mm. at 3700 Å). The absorption path was 0·005—1 m. atm. (to 0·1 m. atm. only with [$^2H_2$]formaldehyde) and the effect of temperature was observed qualitatively in tubes heated to 250°. The emission spectrum was excited by a h.f. electrodeless discharge through flowing formaldehyde vapour at a pressure of a few mm. and was recorded in exposures of up to 5 min. with a 0·02-mm. slit. Partial decomposition occurred in the discharge, the spectra of CO (Ångström and Herzberg systems), CH, and atomic hydrogen being excited in addition to the formaldehyde fluorescence; a number of weak fluorescence bands may have been lost in the background. Wavelengths, referred to iron arc standards, were determined with a Pye comparator, and the rotational structure of the bands was measured with a Hilger non-recording microphotometer.

Interpretation of the spectrum.

(i) *The Absorption Spectrum.*—The representation of the fundamentals of a C_s (pyramidal) excited state is $4a' + 2a''$, the breakdown into stretching (ν), deformational (δ), and rocking (γ) modes being

a'		a''
ν (CH)	ν (CO)	ν' (CH)
δ (CH_2)	γ (CH_2)	γ' (CH_2)

Perpendicular and parallel bands both occur in absorption. The latter are relatively weak and have not been recorded previously; under medium dispersion they have a sharp head on the violet side and traces of closely-spaced rotational sub-maxima (probably *R* sub-heads) degrading to the red region. Progressions with the interval ν(CO) are strongly marked in absorption,[13a] the arrangement of the first members (or " origins ") being shown in Fig. 1. The A($\perp$) and *a*($\parallel$) progressions involve only the excited state fundamental ν(CO).* With H·CHO, strong origins occur 824 (B_0), 1322 (C_0), and 2872 (E_0) cm.$^{-1}$ higher in frequency than A_0, the first interval being repeated between the bands F_0 and E_0.

* In the present notation $\perp$ and $\parallel$ bands are distinguished by upper and lower case letters, respectively. The subscript gives the number of quanta of ν(CO) excited in the upper state; all " origins " therefore have subscript zero. The assigned progressions are labelled A (or *a*) to F in order of increasing magnitude of the fundamentals, *excluding* ν(CO), excited in the upper state. Schou's original notation, which is difficult to adapt to changes of assignment, is noted in Table 2.

[6] Emeléus, *J.*, 1926, 2948.
[7] Herzberg and Franz, *Z. Physik*, 1932, **76**, 720; Gradstein, *Z. phys. Chem.*, 1933, *B*, **22**, 384.
[8] (*a*) Schuler, *Physikal. Z.*, 1944, **45**, 61; (*b*) Schuler and Reinebeck, *Z. Naturforsch.*, 1950, **5a**, 604; (*c*) Dyne, *J. Chem. Phys.*, 1952, **20**, 811.
[9] See Dyne, ref. 8(*c*), and earlier references.
[10] Walsh, *J.*, 1953, 2306.
[11] Brand, *Chem. and Ind.*, 1955, 167.
[12] *Idem*, *Trans. Faraday Soc.*, 1954, **50**, 431.

TABLE 1. *A′ Fundamental frequencies of excited formaldehyde.*

Fundamental		Spectral interval (cm.$^{-1}$) H·CHO	D·CHO	D·CDO
ν(CH) ...	$E_0 - A_0$	2872	—	2078
ν(CO) ...	$A_1 - A_0$	1182	1188	1176
	$B_1 - B_0$	1204	1182	1178
	$a_1 - a_0$	1172	—	1178
	$b_1 - b_0$	1187	1195	1174

Fundamental		Spectral interval (cm.$^{-1}$) H·CHO	D·CHO	D·CDO
$\delta(CH_2)$	$C_0 - A_0$	1322	—	missing
	$d_0 - b_0$	1318	1071	989
$\gamma(CH_2)$ $1^- - 0^-$	$B_0 - A_0$	824	701	604
	$F_0 - E_0$	817	—	598
$1^+ - 0^+$	$b_0 - a_0$	540	458	386

Rotational constants of excited formaldehyde.[3]

Band	A_0	B_0	A_1	C_0	B_1	A_2
ν_0	28,312·7	29,136·6	29,495·1	29,634·5	30,340·1	30,658·7
$A'_{[v]}$	8·749	8·613	8·701	8·893	8·24	8·653
$D'_{[v]}$	1·067	1·067	1·056	1·066	1·055	1·046

The 1180 [$= \nu$(CO)] cm.$^{-1}$ and 1320 cm.$^{-1}$ frequencies are present in the parallel system of bands, together with a new interval (540 cm.$^{-1}$) which appears in place of 824 cm.$^{-1}$. The assignments suggested for all these frequencies are in Table 1, although a closer examination of the 824 and 540 cm.$^{-1}$ intervals, at present grouped together under $\gamma(CH_2)$, is deferred to a later section (cf. Fig. 3). The information obtained from the parallel system is rather limited, owing to the low intensity of the bands; thus the *e* progression of parallel bands was not observed, probably because it is hidden by the broad and much stronger bands of the E progression, and the *a* bands are partly covered in absorption by the A progression.

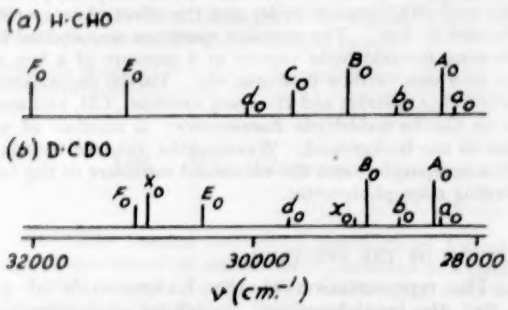


FIG. 1. *Active origins in the absorption spectrum of formaldehyde.*

The assignment of the A, B, and C progressions is supported by the upper-state rotational constants[3] of the A_0, B_0, A_1, C_0, B_1, and A_2 bands of [$^1H_2$]formaldehyde. The appropriate constants are summarised at the foot of Table 1. In first approximation the constant $D = (B + C)/2$ is determined by the C–O bond length, and therefore is sensitive to the quantum level of ν(CO) but not to the principally hydrogen vibrations; accordingly, we find $D'_{[v]} = 1{\cdot}067 \pm 0{\cdot}001$ cm.$^{-1}$ for the origins A_0, B_0, and C_0, the decrement being $\sim$0·01 cm.$^{-1}$ per quantum in higher members of the progressions. The constants $A'_{[v]}$ are somewhat less regular (particularly in the B progression, which is subject to a rotational perturbation) but it is noteworthy that the highest value is for the band C_0. This is consistent with the assignment of $C_0 - A_0$ to the fundamental $\delta(CH_2)$ which is the only vibration expected to lead on excitation to an increment in $A'_{[v]}$.

Band frequencies in absorption are listed in Table 2, the recorded frequency being for the strongest " line " of the partially resolved envelope of a perpendicular band, or for the sharp *R* head of a parallel band. The present assignments are limited to the region between 28,000 and 34,000 cm.$^{-1}$; at higher frequencies the bands are predissociated and finally become diffuse. The transitions in Table 2 are non-temperature sensitive, emanating from the vibrationless ground state. The temperature-sensitive absorption bands are more conveniently classed with the fluorescence system (Table 3).

The weak C progression is apparently missing from the spectrum of [$^2H_2$]formaldehyde, but the interval $d_0 - b_0 = 989$ cm.$^{-1}$ has approximately the correct isotopic shift and is

TABLE 2. *Band centres in the absorption spectrum of formaldehyde.*

Notation		Frequency (cm.$^{-1}$)		Notation		Frequency (cm.$^{-1}$)	
This paper	Schou	H·CHO	D·CDO	This paper	Schou	H·CHO	D·CDO
a_0	—	28,196[a] (*ww*)	28,309[a] (*ww*)	B_2	D′	31,533 (*ms*)	31,319 (*s*)
A_0	A	28,315 (*m*)	28,377 (*m*)	x_2	—	—	31,390 (*www*)
b_0	—	28,736 (*ww*)	28,695 (*ww*)	A_2	D	31,804 (*ms*)	31,853 (*s*)
B_0	B′	29,137 (*m*)	28,981 (*m*)	b_2	—	—	31,025 (*ww*)
x_0	—	—	29,081 (*www*)	F_0	E‴	32,004 (*mw*)	31,053 (*w*)
a_1	—	29,368[a] (*ww*)	—	E_1	E″	32,363 (*m*)	31,616 (*mw*)
A_1	B	29,496 (*ms*)	29,553 (*ms*)	X_1	—	—	32,122 (*m*)
C_0	C‴	29,694[b] (*w*)	—	B_3	E′	32,701 (*s*)	32,455 (*s*)
b_1	C″	29,923 (*ww*)	29,869 (*ww*)	A_3	E	32,930 (*s*)	32,970 (*ss*)
d_0	C″	30,054 (*ww*)	29,684 (*ww*)	F_1	F‴	33,168 (*m*)	32,229 (*mw*)
B_1	C′	30,343 (*m*)	30,159 (*ms*)	E_2	F″	33,536 (*s*)	32,754 (*m*)
x_1	—	—	30,244 (*www*)	X_2	—	—	33,284 (*ms*)
a_2	—	30,524[a] (*ww*)	—	B_4	F′	33,868 (*s*)	33,583 (*s*)
A_2	C	30,659 (*ms*)	30,710 (*s*)	F_2	—	—	33,380 (*mw*)
C_1	D‴	30,875[b] (*w*)	—	E_3	—	—	33,876 (*m*)
E_0	D″	31,187 (*mw*)	30,455 (*w*)	A_4	F	34,035 (*ss*)	34,082 (*s*)
X_0	—	—	30,945 (*mw*)				

s = strong, *m* = medium, *w* = weak, etc.

[a] Band partly covered by the red branches of the neighbouring *A*-band. [b] *R*-head of the $K'' = 3$ sub-band. The band centre is covered by the violet branches of the adjacent *A*-band.

assigned provisionally to $\delta(CD_2)$. The X progression of [$^2H_2$]formaldehyde ($X_0 - A_0 = 2568$ cm.$^{-1}$) has no obvious counterpart in the spectrum of the light molecule and is difficult to assign. Ostensibly, a 2568 cm.$^{-1}$ interval might (with allowance for anharmonicity) be identified with $2\delta(CD_2) + 600 = 2578$ cm.$^{-1}$, but if this is correct it is difficult to see why $2\delta(CD_2)$ is not itself an active interval in the spectrum. The weak *x* progression (‖) falls close to the B progression and is almost certainly covered by this progression in the spectrum of [$^1H_2$]formaldehyde. (The rotational perturbation known to affect the B_0 and B_1 bands of [$^1H_2$]formaldehyde may be due to coupling with the upper state of a neighbouring *x* band.) It is consistent with the selection rules to assign $x_0 - A_0 = 704$ cm.$^{-1}$ to the *a*″ fundamental $\gamma'(CD_2)$.

A few, very weak bands are visible between 28,000 and 25,300 cm.$^{-1}$; they are not intensified by temperature and look different from the bands of the 28,000 cm.$^{-1}$ system. These bands must belong to a separate electronic transition, presumably [13] to the T ⟵ S transition corresponding to the stronger S ⟵ S system at 28,000 cm.$^{-1}$.

(2) *The Fluorescence Spectrum*: *Vibrational Structure.*—An interesting aspect of the fluorescence spectrum is the extreme weakness of transitions to the vibrationless level of the ground state; band A_0, for example, has not been detected in emission with H·CHO and is very feeble with D·CDO. The strongest fluorescence bands combine with ground-state levels in which several quanta of the vibration $\nu_6''(b_2)$ are excited; and this is an immediate argument in favour of a nonplanar excited state, as was first perceived by Walsh.[10]

The fluorescence bands are all perpendicular. The carbonyl vibration, $\nu_2''(a_1)$, is active in forming progressions which, when well developed, run positively for several members and negatively for one or two members, the origins being arranged in a regular manner (Fig. 2) that has no obvious resemblance to the corresponding diagram for the absorption spectrum. Two principal (α and β) and two subsidiary (γ and δ) systems of bands can be distinguished, all the bands of a given system (apart from the members of the negatively-running progressions) emanating from the same upper-state level.* The absorption band A_0, in spite of its weakness in emission, is the hinge of the whole spectrum; the origins of the β system are spaced out at intervals of $2\nu_6''$, commencing with A_0, and terminate on the *even-numbered* levels ($n_6'' = 0, 2, 4\ldots$) of a stack of ν_6'' quanta built up from the vibrationless level of the ground state. These transitions are designated

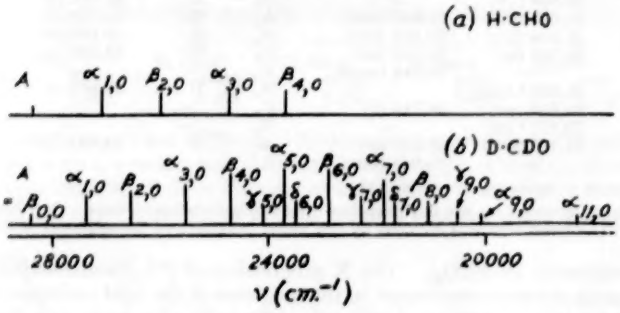
$$\beta_{0,0}\ (= A_0),\ \beta_{2,0},\ \beta_{4,0}\ldots$$

* The fluorescence spectrum of [$^2H_2$]formaldehyde is less well-developed than that of [$^2H_2$]formaldehyde and shows the principal α and β systems only.

[13] Cf., however, Reid, *J. Chem. Phys.*, 1953, **21**, 1906.

the first and second subscripts denoting, respectively, the quantum levels of ν_6'' and ν_2''. All the bands of the β system therefore terminate on ground state A_1 vibrational levels. The α system develops from the band $\alpha_{1,0}$ (band " α " in Schou's original notation) and consists of transitions to the *odd-numbered* (B_2) quantum levels of ν_6''. The evidence for these assignments is, at present, that the interval between consecutive members in a band system, allowing for a regular decrement due to anharmonicity, is always $2\nu_6''$; but in the following section a characteristic difference in the rotational structure of the α and β bands

FIG. 2. *Vibrational structure of the fluorescence spectrum.*



The transitions shown are origins of progressions in the carbonyl-stretching frequency, ν_2''. The α- and γ-bands terminate on odd-numbered, and the β- and δ-bands on even-numbered, levels of the planar deformation vibration, ν_6'', of the ground state.

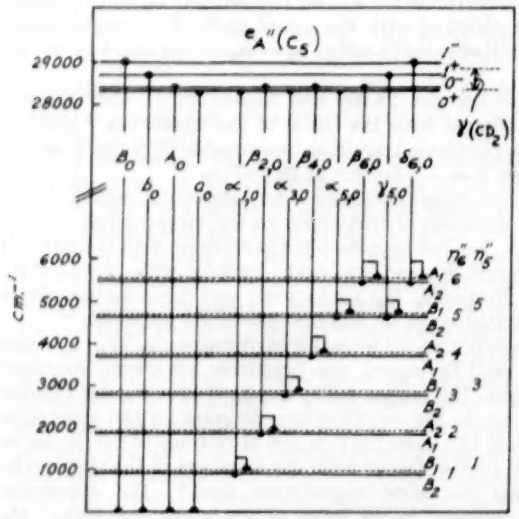


FIG. 3. *Vibronic states and transitions of* [$^2H_2$]*formaldehyde.*

is shown to confirm this conclusion beyond doubt. The height of the upper level of the α bands can be evaluated from $\nu(\alpha_{1,0}) + \nu_6''$, $\nu(\alpha_{3,0}) + 3\nu_6''$, etc., and comparison with the absorption frequencies shows that the parallel transition a_0 is almost certainly a transition to the same upper state. The δ bands of [$^2H_2$]formaldehyde lie 600 cm.$^{-1}$ to the violet of the β bands and this interval is identical with $B_0 - A_0$ in absorption (Table 1); the δ bands, therefore, have the same upper state as B_0. Similarly, the γ system of [$^2H_2$]formaldehyde is found 385 cm.$^{-1}$ above the α system (cf. $b_0 - a_0 = 386$ cm.$^{-1}$; Table 1)

and the upper state of the γ bands is common with that of b_0. These relations are summarised in Fig. 3. The γ and δ bands are weakened in emission by their Boltzmann factors and appear only in the strong, central region of the spectrum.

The frequencies of the band centres in the fluorescence spectrum are listed in Table 3. Only two ground-state vibrations, ν_2'' and ν_6'', are active in fluorescence, and the fundamentals, anharmonic terms, and zero-order frequencies are noted in Table 4. The anomalies in the anharmonic terms (*e.g.*, $x_{66}^{D\cdot CDO}$ is $> x_{66}^{H\cdot CHO}$) are due to the substitution of band centres for the true gyrovibronic origins, and the product-rule calculation has a small defect (0·6%) for the same reason. The explanation of the poorer development of the

TABLE 3. *Band centres in the fluorescence spectrum of formaldehyde.*

	H·CHO		D·CDO			H·CHO		D·CDO	
Assigt.	Intensity [a]	cm.$^{-1}$	Intensity [a]	cm.$^{-1}$	Assigt.	Intensity [a]	cm.$^{-1}$	Intensity [a]	cm.$^{-1}$
$\alpha_{1,-3}$	—	—	*b*	30,852 [c]	$\gamma_{7,0}$	—	—	5	22,283·2
$\alpha_{1,-2}$	0	29,359 [c]	0	29,708 [c]	$\alpha_{3,2}$	3	21,293·6	3	22,173·8
$\alpha_{1,-1}$	2	28,207	3	28,550 [c]	$\alpha_{5,1}$	—	—	6	22,029·0
$A_0 = \beta_{0,0}$	*b*	28,312·7	00	28,377	$\alpha_{7,0}$	—	—	6	21,898·6
$\beta_{2,-1}$	5	27,173 [c]	4	27,690·0 [c]	$\delta_{8,0}$	—	—	3	21,673·8
$\alpha_{1,0}$		27,035·9 [c]	5	27,372·4 [c]	$\beta_{2,3}$	—	—	2	21,499·2
$\beta_{0,1}$	1	27,569·1 [c]	—	—	$\beta_{4,2}$	1	20,271	2	21,339·5
$\alpha_{1,+1}$	2	26,469·0	—	—	$\beta_{6,1}$	—	—	5	21,200·8
$\alpha_{3,-1}$	—	—	5	26,704·1	$\beta_{8,0}$	—	—	4	21,074·7
$\beta_{2,0}$	4	25,990·9 [c]	6	26,515·4 [c]	$\gamma_{7,1}$	—	—	1	20,628·0
$\beta_{4,-1}$	—	—	4	25,848·0	$\alpha_{3,3}$	—	—	1	20,528·2
$\alpha_{1,1}$	6	25,296·8	5	25,679·2	$\gamma_{9,0}$	—	—	2	20,506·3
$\alpha_{3,0}$	4	24,721·3	7	25,523·7	$\alpha_{5,3}$	—	—	2	20,374·8
$\gamma_{5,-1}$	—	—	2	25,257·2	$\alpha_{7,1}$	—	—	2	20,242·5
$\beta_{2,1}$	6	24,258·5	6	24,823·7	$\alpha_{9,0}$	—	—	1	20,121·8
$\beta_{4,0}$	10	23,687·0	9	24,675·1	$\beta_{6,3}$	—	—	0	19,553
$\alpha_{1,2}$		23,578·7	3	24,003·0	$\beta_{8,1}$	—	—	1	19,422
$\gamma_{5,0}$	—	—	3	24,084·2	$\gamma_{9,1}$	—	—	00	18,864
$\alpha_{3,1}$	6	22,996·6	9	23,840·2	$\alpha_{5,3}$	—	—	0	18,750
$\alpha_{5,0}$	—	—	10	23,698·4	$\alpha_{7,3}$	—	—	0	18,609
$\delta_{6,0}$	—	—	4	23,462·7	$\alpha_{9,1}$	—	—	1	18,479
$\beta_{2,2}$	4	22,547·2	3	23,153·6	$\alpha_{11,0}$	—	—	00	18,366
$\beta_{4,1}$	4	21,970·9	9	22,999·5	$\beta_{8,2}$	—	—	0	17,788
$\beta_{6,0}$	—	—	10	22,863·5	$\beta_{10,1}$	—	—	1	17,673
$\alpha_{1,3}$	3	21,880·6	3	22,345·5					

[a] Visual estimates on a scale of 10. [b] Band observed in absorption only. [c] Observed in fluorescence and as a temperature-sensitive band in absorption.

A − sign preceding the second subscript in the notation (col. 1) indicates a quantum change of the excited state carbonyl vibration, ν(CO); a ± sign indicates a quantum change in both upper and lower states.

TABLE 4. *Ground-state fundamentals and zero-order frequencies.*

	H·CHO		D·CDO	
	Fluorescence spectrum	Infrared spectrum	Fluorescence spectrum	Infrared spectrum
ν_2	1744·7	1743·6 [a]	1704·1	1700 [a]
x_{22}	−10·3	—	−9·0	—
ω_2^0	1755·0 ± 1·2	—	1713·1 ± 1·4	—
ν_6	1163·6	1165 [a]	934·7	933·8 [b]
x_{66}	−2·3	—	−3·1	—
ω_6^0	1165·9 ± 0·6	—	937·8 ± 0·6	—
x_{26}	−6·5	—	−7·0	—

ω_6^0 (HCHO)/ω_6^0 (DCDO) = 1·244 ± 0·003; calc. 1·252.

[a] Herzberg, "Infra-red and Raman Spectra," van Nostrand, New York, 1945, p. 300. [b] Table 6.

spectrum of normal formaldehyde than of that of the deuterated molecule is twofold. First, the most probable transition combining a pyramidal excited state with a planar ground state must involve a greater quantum change of ν_6''(D·CDO) than of ν_6''(H·CHO) owing to the larger vibrational amplitude of the light molecule. This effect is very pronounced, the active vibrational levels running much higher with [$^2H_2$]formaldehyde.

Secondly, with [$^1H_2$]formaldehyde the accidental near-coincidence between $2\nu_2''$ (3490 cm.$^{-1}$) and $3\nu_6''$(3492 cm.$^{-1}$) produces systematic overlapping in the bands of the α and β systems. The coincidence does not lead to a perturbation (the symmetry properties of the levels are different) but when the bands are weak the adjacent transitions are difficult to pick out. Several transitions of [$^1H_2$]formaldehyde are, in fact, visible below 20,000 cm.$^{-1}$ but it has not been possible to disentangle and assign the band centres with any certainty.

The dependence of intensity on the quantum change of ν_2'' and ν_6'' is shown, for [$^2H_2$]formaldehyde, in Table 5. The entries in the horizontal rows refer alternately to β

TABLE 5. *Intensity distribution in the fluorescence bands of* [$^2H_2$]*formaldehyde.*

	n_6'' =	0	1	2	3	4	5	6	7	8	9	10	11
						β and α bands							
n_2'' =	1	—	**3**	4	**5**	4	—	—	—	—	—	—	—
	0	00	5	6	7	9	**10**	**10**	6	4	1	—	00
	1	—	5	6	**9**	**9**	6	5	2	1	1	1	—
	2	—	3	3	3	3	2	0	0	0	—	—	—
	3	—	3	2	1	—	0	—	—	—	—	—	—
						δ and γ bands							
n_2'' =	0	—	—	—	—	—	3	4	**5**	3	2	—	—
	1	—	—	—	—	—	—	—	1	—	00	—	—

(n_6'' even) and α (n_6'' odd) bands; the smoothness of the intensity distribution shows that the $|\psi_{ev}|^2$ function must have nearly the same shape in the upper levels of both systems. Compared with the α and β systems, the strongest transitions of the γ and δ series are to appreciably higher levels of ν_6''.

(3) *The Fluorescence Spectrum: Rotational Structure.*—(a) [$^1H_2$]*Formaldehyde.* The $\alpha_{1,0}$ band of [$^1H_2$]formaldehyde (Fig. 4*a*) was discussed in an earlier paper.[14] The prominent lines in the sub-bands of the violet region are *rR* heads, the *rQ* branches being by comparison much less prominent owing to the red shading of the band; the pattern is not repeated on the red side of the band origin because of the intrinsic weakness of the *pR* branches. The *K*-numbers of the violet sub-bands deduced in the previous paper have been confirmed by high-dispersion measurements,[8c] and the conclusion that sub-bands with *even* K'' are *strong* proves that the lower state of the transition is B_1 or B_2. From the appearance of the first violet sub-band, in the region where the limiting symmetric top formulæ are inadequate, it is almost certain that the band is type B. Finally, the high-dispersion measurements establish that the band is really double; Coriolis coupling of the fundamentals $\nu_5''(b_1)$ and $\nu_6''(b_2)$ mixes the characters of the two levels and the band marks an unresolved pair of transitions to the b_2 components in each of the resultant states (Fig. 3). As in quite recent papers the lower level of $\alpha_{1,0}$ has been identified with the vibrationless ground state [8b] and with the upper level of the fundamental $\nu_5''(b_1)$,[10,15] it is worth emphasing that the evidence for its assignment to a b_2 state is overwhelming.

The transitions to higher vibrational levels of ν_6'' show that there is systematic coupling between the overtones $n\nu_5''$, $n\nu_6''$ with n odd, and between the overtone and combination levels $2n\nu_6''$, $n\nu_5'' + n\nu_6''$ with n integral (but excluding zero). The first type of coupling affects the lower levels of the α, and the second the lower levels of the β bands; in both cases the product of the symmetry species of the coupled levels is A_2 and the coupling perturbs the normal dependence of the rotational energy levels on K''. In this respect the rotational structure of the fluorescence bands closely resembles the ν_5,ν_6 infrared fundamental.

In the β system of fluorescence bands, sub-bands with *odd* K'' are *strong* and the lower state is therefore A_1 or A_2, in agreement with purely vibrational evidence (Section 2) which requires A_1 lower states. This point is illustrated for the $\beta_{2,0}$ band in Fig. 4*c*, where it can be seen that the $K'' = 1$ sub-band (split by the asymmetry into two heads 6 cm.$^{-1}$ apart) is strong. As the spacing of the sub-bands is abnormal, indicating Coriolis coupling,

[14] Brand, *Trans. Faraday Soc.*, 1950, **46**, 805.
[15] Walsh, *J. Chem. Phys.*, 1952, **20**, 1502.

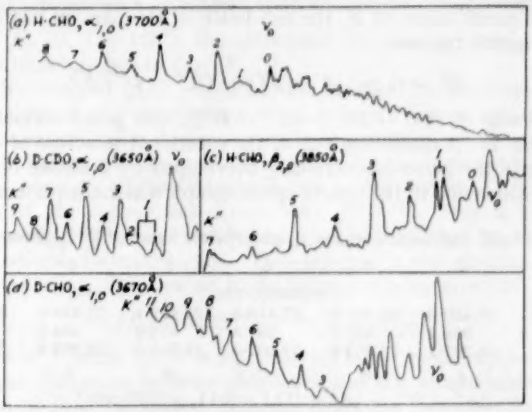
it is inferred that each of the β bands marks a double transition terminating on mixed A_1 and A_2 lower states, the higher-frequency component being to the even-numbered (mainly A_1) overtones of ν_6''.

(b) [$^2H_2$]*Formaldehyde.* To number the sub-bands of the $\alpha_{1,0}$ band of [$^2H_2$]formaldehyde it is necessary first to know the numbering of the ν_5', ν_6' ground-state fundamental which hitherto has not been analysed. For the fundamental, neglecting the effect of asymmetry (valid for $K' \ll 3$) and assuming the same rotational constants in the upper and lower states, Nielsen's equation [16] for the sub-band frequencies is:

$$\nu_{0\,(\delta,\epsilon)}^{\mathrm{Sub}} = (\nu_5' + \nu_6')/2 + \zeta^2 A - (A - D) \pm 2(A - D)K'^2 \pm [(\nu_5' - \nu_6')^2/4 - (2A\zeta K')^2]^{\frac{1}{2}} \quad . \quad (1)$$

The first ± symbol in equation (1) refers to transitions with $\Delta K = \pm 1$, and the second distinguishes the two states arising from the rotational coupling. Apart from the complex

FIG. 4.



region between the origins, the + and − signs are taken in phase, ++ in the violet sub-bands and −− in the red. In these branches the sub-band frequencies can be expressed as sums and differences: [17]

$$(\nu_{++} + \nu_{--})/2 = (\nu_5' + \nu_6')/2 + \zeta^2 A - (A - D) \quad . \quad . \quad . \quad . \quad (2)$$

and

$$[(\nu_{++} - \nu_{--})/2 - 2K'(A - D)]^2 = (\nu_5' - \nu_6')/2 + 4A^2\zeta^2 K'^2 \quad . \quad . \quad (3)$$

where in each case ν_{++} and ν_{--} refer to sub-bands with the same K'. The analysis requires prior knowledge of A and D which in this paper are calculated from the rotational constants for [$^1H_2$]formaldehyde;[3] as this demands an appeal to the molecular geometry only for the smaller constant D, the values are probably accurate to 0·02 cm.$^{-1}$. A least-squares treatment of the experimental frequencies [18] using equations (2) and (3) leads to the results in Table 6;* agreement with the value of ν_6'' deduced from the fluorescence spectrum (Table 4) is satisfactory.

The procedure for numbering the sub-bands of the $\alpha_{1,0}$ band is as follows. As the upper state of the ν_5', ν_6' fundamental is identical with the lower state of $\alpha_{1,0}$, the Kth R sub-head of the parallel transition connecting the vibrationless ground state with the upper level of $\alpha_{1,0}$ (*i.e.*, the absorption band a_0) is found by adding the frequency of the

* Eqns. (1)—(3) enable the two origins of the ν_5', ν_6' band to be calculated, without discriminating between them. The identification of ν_6'' with the 934 cm.$^{-1}$ frequency follows from the product rule (Table 4).

[16] Nielsen, *J. Chem. Phys.*, 1937, **5**, 818.
[17] Davidson, Stoicheff, and Bernstein, *ibid.*, 1954, **22**, 289.
[18] Ebers and Nielsen, *ibid.*, 1938, **6**, 311.

TABLE 6. *Analysis of the* ν_5, ν_6 *(ground state) fundamental of* [$^2H_2$]*formaldehyde.*

A = 4·705, D = 1·001 cm.$^{-1}$.[a]

K'		3	4	5	6	7	8	9
		Frequency, cm.$^{-1}$						
ν_{+}	obs.[b]	1014·4	1023·3	1033·3	1043·4	1053·8	1066·4	—
	calc.	1013·3	1023·2	1033·3	1043·7	1055·5	1065·9	1076·9
ν_{-}	obs.[b]	906·4	893·3	887·8	875·9	864·9	852·9	841·3
	calc.	905·6	895·9	886·7	875·2	864·3	853·2	841·9
Intensity		*s*	*w*	*s*	*w*	*s*	*w*	*s*

$\nu_5 = 933{\cdot}8$ cm.$^{-1}$, $\nu_6 = 990{\cdot}4$ cm.$^{-1}$, $\zeta = 0{\cdot}498$.

[a] Calculated from the rotational constants of [$^1H_2$]formaldehyde. [b] Ebers and Nielsen, ref. 18.

—— sub-band of ν_5, ν_6 with $K'' = K$ to the *rR* head of the sub-band of $\alpha_{1,0}$ with $K' = K$ (Table 7). Because the sum must be consistent with the measured frequency of band a_0, only one set of numbers for the sub-bands of $\alpha_{1,0}$ is acceptable (Fig. 4*b*). Moreover, for not too large or too small values of K, the sub-heads of the parallel band obey the usual equation for a symmetric top, *viz.*,

$$\nu_R^{sub} = \nu_R^0 + [(A' - D') - (A'' - D'')]K^2 \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The least-squares value of $[(A' - D') - (A'' - D'')]$, one point seriously off line being neglected, is in Table 7. A direct analysis of the rotational structure of a_0 was not undertaken, partly because the band was seriously overlapped by a strong neighbour (A_0) and partly because the dispersion of the quartz spectrograph was inadequate in this region.

TABLE 7. qR *Sub-heads in the* a_0 *absorption band of* [$^2H_2$]*formaldehyde.*

K		4	5	6	7	8	9	10
		Frequency, cm.$^{-1}$						
$\alpha_{1,0}$, *rR* Head		27,400·9	27,410·3	27,419·8	27,429·5	27,439·0	27,448·1	27,457·3
ν_5, ν_6, *pQ* Branch[a]		906·4	893·3	887·8	875·9	864·9	852·9	841·3
ν_R^{sub}		28,307·3	28,303·6	28,307·6	28,305·4	28,303·9	28,301·0	28,298·6
Intensity		*s*	*w*	*s*	*w*	*s*	*w*	*s*

$[(A'' - D'') - (A' - D')] = 0{\cdot}11_9 \pm 0{\cdot}03$ cm.$^{-1}$.

[a] Ebers and Nielsen, ref. 18.

The intensity alternation in the $\alpha_{1,0}$ band of [$^2H_2$]formaldehyde, compared with [$^1H_2$]formaldehyde, is reversed by the change in nuclear statistics. Asymmetry is apparent in the sub-bands with $K'' < 2$, the probable assignment of the various maxima being indicated in Fig. 4*b*. The splitting of the $K'' = 1$ sub-band is in better agreement with the calculated value if the band is type B rather than type C. Coriolis coupling in the lower state doubles each of the transitions in fluorescence (Fig. 3), as already described for [$^1H_2$]formaldehyde. The rotational structure is well marked in the fluorescence spectrum to about 22,000 cm.$^{-1}$, but at lower frequencies, and especially below 20,000 cm.$^{-1}$ where the bands are very weak, only the band centres and one or two rotational sub-maxima are visible. Among the well-developed bands it is easily verified that the α and γ bands have the same intensity alternation as $\alpha_{1,0}$, and that the β and δ bands have qualitatively the same rotational structure but with the intensity alternation reversed. The previous conclusion, that the α and β bands have respectively *B* and *A* lower states, is therefore confirmed completely.

(c) [$^2H_1$]*Formaldehyde.* The microphotometer record of the $\alpha_{1,0}$ band of [$^2H_1$]formaldehyde is reproduced in Fig. 4*d*. The intensity distribution is different from the corresponding bands of the symmetrically substituted formaldehydes, the apparent band centre (or strongest "line," ν_0) being farther to the red, and the violet sub-bands weaker than with either of the other isomers. The explanation, however, is simply that the $\nu_5''(a')$ fundamental of [$^2H_1$]formaldehyde is lower in frequency than $\nu_6''(a'')$,[17] the order in which the pair of transitions of the composite ultraviolet band appear in the spectrum being reversed. The band centre still marks the transition terminating in emission on the $\nu_6''(a')$ component of the coupled state, as in the spectra of the symmetrical isomers; but

the violet sub-bands now belong to the transition combining the upper state with the essentially $\nu_5''(a')$ component of the lower state, and their origin is some 25 cm.$^{-1}$ higher in frequency than the band centre. The violet sub-heads are numbered by the method described for [$^2H_2$]formaldehyde, using the analysis of the ν_5,ν_6 fundamental recently published by Davidson *et al.*[17]

(4) *Rotational Constants of the Excited State.*—Although the rotational constants of several excited vibronic levels of [$^1H_2$]formaldehyde are known from high-dispersion measurements (cf. Table 1), values for at least two isotopically substituted species are required for a full structure determination. In the present analysis, the first step is to evaluate $[(A' - D') - (A'' - D'')]$ using equation (4) and the particular combination of infrared and ultraviolet frequencies represented (for D·CDO) in Table 7. The double prime then refers to the vibrationless ground state, and the single prime to the lowest vibrational level of the excited state (0^+ in Fig. 3). As the ground-state constants are completely known only for [$^1H_2$]formaldehyde, $D_{[v]}''$ for [$^2H_2$]formaldehyde and $A_{[v]}''$ and $D_{[v]}''$ for [$^2H_1$]formaldehyde were calculated from the probable molecular geometry (r_{CH} = 1·08$_9$, r_{CO} = 1·21$_5$ Å, $\widehat{HCH}$ = 120°), the estimated uncertainty being about 0·03 cm.$^{-1}$ in $A_{[v]}''$ and proportionately less in $D_{[v]}''$.*

The values of the constant $(A_{[v]}' - D_{[v]}')$ found by this treatment are in Table 11.

Approximate values of $D_{[v]}'$ were obtained as follows. Under medium dispersion the rR-branches of the perpendicular fluorescence bands abruptly lose sharpness and much of their intensity when, by the cancellation of lines ($J \nless K$), the higher sub-bands fail to form heads. For the $\alpha_{1,0}$ band of [$^1H_2$]formaldehyde this is observed for $K'' \geqslant 7$, and it follows that the inflection of the R-branches occurs with $J'' = 7$. This is known from high-dispersion measurements to be correct [8c] and the method can be applied with some confidence to the isotopic formaldehydes. Convergence in the rR-branches is controlled by $(D_{[v]}'' - D_{[v]}')$, the value of J'' nearest to the inflection being given by

$$2/(2J'' + 3) \approx (D_{[v]}'' - D_{[v]}')/D_{[v]}'' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

When applied to the $\alpha_{1,0}$ bands, $D_{[v]}''$ in equation (5) refers to the upper level of the ν_5,ν_6 fundamental. If the difference between this level and the vibrationless ground state is neglected, the value of $D_{[v]}''$ calculated from the molecular geometry can be substituted in equation (5); $D_{[v]}'$ is then found directly from the spectra (Table 11).

The rotational constants found by these methods do not, of course, approach the accuracy of high-dispersion measurements. For the time being, however, they represent a coherent set of values for the three isotopically substituted formaldehydes.

Discussion

(5) *Selection Rules for Transitions between a Planar Ground State and a Non-planar Excited State.*—The ground state of an isotopically symmetrical formaldehyde is C_{2v}. On the assumption that the C–H bonds are equivalent, the non-planar state is C_s, the potential field retaining the higher symmetry (C_{2v}) on account of the inversion. In both states the molecule is a near-prolate symmetric top ($I_a \ll I_b, I_c$) and the rotational levels can be classified by the approximate quantum number K: this is a useful classification experimentally for, under medium dispersion, the transitions with different K are resolved whereas those with different J are not.

The overall selection rules [19] are

$$\Delta J = 0, \pm 1, \quad + \longleftrightarrow -, \quad s \longleftrightarrow s, \quad a \longleftrightarrow a$$

In the C_s state the inversion doubling gives rise to pairs of levels wherein one sub-level is + and the other − with respect to inversion. The corresponding s,a characters are found from the expression

$$P(\psi) = I(\psi) \,.\, C_2^b(\psi_r) \,.\, \sigma_{ac}(\psi_{er}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

* With these parameters the calculated value of $(A_{[v]}'' - D_{[v]}'')$ for [$^2H_1$]formaldehyde is 5·49$_8$ cm.$^{-1}$. Experimental measurement [17] gives 5·47 ± 0·3 cm.$^{-1}$.

[19] Herzberg, "Infrared and Raman Spectra," Van Nostrand, New York, 1945, p. 50.

where $I(\psi)$ and $P(\psi)$ denote the operations of inversion and permutation of identical nuclei, the factor $C_2^b(\psi_r)$ rotates the molecule by π about the b-axis, and $\sigma_{ac}(\psi_{es})$ reflects the electronic co-ordinates and the nuclear displacements in the plane of the a,c axes. The last two factors contribute a product of ± 1 depending on the species of the rotational and vibronic wave-functions. It follows immediately from equation (6) that the rotational manifold of one inversion doubling sub-level of an A' vibronic state has the identical $+,-$ and s,a characters as an A_1 ground vibronic state, the other having the characters of a B_2 state. Similarly, the A'' inversion doublets have collectively the same characters as the A_2 and B_1 ground vibronic states. This result might have been foreseen intuitively for, as the non-planar equilibrium configuration is straightened out, the inversion doublets must go over into a quantum of the $\nu_6(b_2)$ fundamental of the planar molecule.

Transitions allowed by the overall selection rules are listed in Table 8. The transitions in cols. 1—3 are free from any restriction, but those in col. 4 are forbidden by the rotational selection rules for an asymmetric top; they will not appear if the species of the rotational wave-function is pure, but may do so if mixing occurs by a suitable perturbation. The rules in Table 8 are formally the same as those governing the combination of two C_{2v} states. Owing to the different statistical weight of the s and a levels, the sub-bands of a transition will display the usual alternation of intensity with K, whether the inversion doubling is resolved or not.

TABLE 8.

ΔK odd ($\perp$)		ΔK even ($\parallel$)	
c-axis	*b*-axis	*a*-axis	forbidden
$A_1 \longleftrightarrow A'(-)$	$A_1 \longleftrightarrow A''(-)$	$A_1 \longleftrightarrow A'(+)$	$A_1 \longleftrightarrow A''(+)$
$A_2 \longleftrightarrow A''(-)$	$A_2 \longleftrightarrow A'(-)$	$A_2 \longleftrightarrow A''(+)$	$A_2 \longleftrightarrow A'(+)$
$B_1 \longleftrightarrow A''(+)$	$B_1 \longleftrightarrow A'(+)$	$B_1 \longleftrightarrow A''(-)$	$B_1 \longleftrightarrow A'(-)$
$B_2 \longleftrightarrow A'(+)$	$B_2 \longleftrightarrow A''(+)$	$B_2 \longleftrightarrow A'(-)$	$B_2 \longleftrightarrow A''(-)$

The symbols (+) and (−) following the C_s species classification distinguish the *vibronic* sub-levels arising from the inversion doubling. (+) States correlate with the A states of the rotational sub-group (C_s) of the planar molecule, and (−) with B.

For [$^2H_1$]formaldehyde, the non-planar state has no symmetry element (C_1). If the inversion doubling is resolved, however, one sub-level will behave as A' and the other as an A'' vibronic state of the point-group C_s. The intensity alternation vanishes, as can be seen from Fig. 4*d*.

(6) *Vibrational Analysis.*—The analysis in terms of a pyramidal excited state offers no serious difficulty. The crucial point is the interpretation of four low-lying levels of the excited state, which are now assigned in pairs to the inversion doubling the sub-levels of the zeroth (0^+, 0^-; cf. Walsh [10]) and first (1^+, 1^-) vibrational levels of the fundamental $\gamma(CH_2)$ (Table 9). The vibration frequency is found approximately from the separation of the centres of the inversion doublets.

TABLE 9.

Upper level of fluor. system		α	β	γ	δ
Height (cm.$^{-1}$)	H·CHO	0	124 •	540	947
	H·CDO	0	93	458	794
	D·CDO	0	67	385	671
Assigt. γ (CH_2)		0^+	0^-	1^+	1^-

• The gyrovibronic origin of A_0 (Table 1) and the R-head of band a_0 (ν_R^0; eqn. 4) are separated by 28,312·7 − 28,198·0 = 115·7 cm.$^{-1}$. To find the separation of the *origins* we add 8·8 cm.$^{-1}$, representing the calculated interval between the R-head and gyrovibronic origin of a_0. The corresponding values for the isotopic formaldehydes are uncorrected.

The transitions connecting the ground A_1 vibronic state with the 0^- and 1^- upper vibronic levels are known [3] to be type B, and the species of the upper levels is therefore $A''(-)$ (Table 8). Similarly, the transitions between the B_2 ground vibronic states and the 0^+ and 1^+ levels almost certainly are also type B, and the (+) upper levels must be $A''(+)$. Granted this, the species of the upper state orbital wave-function is A''. The fact that $\parallel$ transitions connect the A_1 ground state with the 0^+ and 1^+ upper states is supplementary evidence of their (+) character [if they were (−) levels the transitions

would be forbidden by the strict $s \leftarrow\!\!\!\!\!\!\rightarrow a$, $+ \leftarrow\!\!\!\!\!\!\rightarrow +$, and $- \leftarrow\!\!\!\!\!\!\rightarrow -$ prohibition], but the full explanation is not quite straightforward for the $A''(+) \longleftarrow A_1$ transitions are forbidden by the asymmetric top rules (Table 8). As the combination $A'(+) \longleftarrow A_1$ is allowed by both the asymmetric top and the overall selection rules it seems likely that the predominantly $A''(+)$ states have some admixed $A'(+)$ character; and although the identity of the perturbation is uncertain it may be connected with the state which induces predissociation in the absorption bands at higher frequencies.

In an $A'' \longleftarrow A_1$ transition the quantum change of the $\gamma(CH_2)$ vibration is unrestricted by the selection rules. The $\nu_6(b_2)$ ground state vibration is unlimited as to *even* quantum changes, the odd levels being allowed to combine with (+) upper states and the even levels with (−). Apart from this peculiar restriction, the spectral activity of both vibrations is controlled by the Franck–Condon principle.[20] Experimentally, the two vibrations are active in a strikingly different way for, whereas the ground-state vibration changes by as many as 10 quanta, the $\gamma(CH_2)$ fundamental is active only in the zeroth and first levels. This is largely the Franck–Condon effect. If the transitions in fluorescence are considered first, it is clear that the overlap between the vibronic level of the bent upper state and the ground state is greatest when several quanta of $\nu_6(b_2)$ are excited. With [$^2H_2$]formaldehyde the intensity maximum corresponds to $n_6'' = 5$ or 6 in transitions from the 0^+ and 0^- levels (α and β bands), and to $n_6'' = 6$ or 7 in transitions from the higher 1^+ and 1^- levels (γ and δ bands: Table 5). The similarity in intensity distribution among the α and β bands follows naturally from the fact that the pair of upper levels is simply an inversion doublet. In absorption, however, the position is different because, owing to the inversion doubling, the overlap between the wave-functions of the vibrationless ground state and the levels of $\gamma(CH_2)$ in the excited state does not pass through a maximum; rather it decreases progressively from the zeroth level of $\gamma(CH_2)$ upwards, and only the transitions to the zeroth and first levels are recorded in the spectrum.

The *a'* excited-state fundamentals of the symmetrically substituted formaldehydes are assembled in Table 10, together with incomplete results for [$^2H_1$]formaldehyde. The product-rule ratio is not entirely satisfactory, for the defect is in the wrong direction; probably the evaluation of $\gamma(CH_2)$ from the centres of the inversion doublets is rather a poor approximation to the zero-order frequency. The present measurements do not give a direct indication of the multiplicity of the excited state, but the oscillator strength of the spectrum of an ether solution [21] is about 5×10^{-4} and it seems certain that there is no multiplicity change in the transition. The excited electronic wave-function can therefore be specified as $^1A''$. The electronic origins, measured to the centre of the 0^+ and 0^- inversion doublet, are noted in Table 10.

TABLE 10. *Electronic origin and a' fundamentals of excited formaldehyde.*

	H·CHO	H·CDO	D·CDO
ν_0	28,252	28,303	28,343
ν(CH)	2875	—	2078
$\delta(CH_2)$	1322	1071	989
ν(CO)	1182	1188	1176
$\gamma(CH_2)$	682	579	494

$\Pi\{\nu(\text{D·CDO})/\nu(\text{H·CHO})\} = 0{\cdot}39$ (calc.: 0·41).

(7) *Stereochemistry of the Excited State.*—(a) *The asymmetry parameter.* The asymmetry parameter, $\delta = (B - C)/(A - C)$, of the excited state of the absorption bands analysed by Dieke and Kistiakowsky [3] is 0·0145. (The states in question include the 0^- and 1^- levels discussed in Section 6; between one level and another there is a small variation of δ which probably does not exceed the experimental error.) This value is appreciably smaller than in the ground state ($\delta = 0{\cdot}0195$; Lawrance and Strandberg [22]) and is actually too low to be consistent with a planar upper state. Dieke and Kistiakowsky explained the defect by a rotational perturbation, but the assumption of a non-planar upper state removes the

[20] Herzberg and Teller, *Z. phys. Chem.*, 1933, *B*, **21**, 410.
[21] Reiche and Meister, *Ber.*, 1935, **68**, 1465.
[22] Lawrance and Strandberg, *Phys. Rev.*, 1951, **83**, 363.

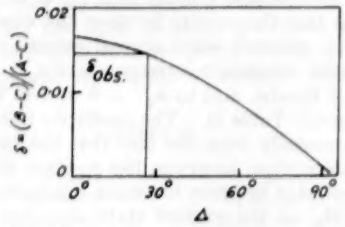
difficulty altogether. The variation of the asymmetry parameter with Δ, the angle between the plane of the CH_2 nuclei and the C–O axis, is shown in Fig. 5 for trial structures wherein the geometrical parameters were chosen to fit the experimental rotational constants. The recorded value of δ corresponds to $\Delta = 25$—$30°$.

(b) *The inversion doubling splitting.* An independent value of Δ can be found [23] from the inversion doubling splitting, $\Delta\nu = 0^- - 0^+$, and the fundamental frequency $\gamma(CH_2)$. The potential, assumed harmonic, is given by

$$V = \tfrac{1}{2}k_\Delta(\Delta - \Delta_e)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Δ_e being the equilibrium value of Δ. k_Δ is approximately a valence force constant if the equilibrium configuration is not too strongly bent. The potential defined by equation (7) leads to a double-minimum function with a cusp at the centre; the real barrier must be rounded and somewhat lower, but the error is probably not serious because the amplitude

FIG. 5.



of the vibrational wave-function is small in this region. Two assumptions which further simplify the calculation are: first, that the $\gamma(CH_2)$ vibration does not interact appreciably with the other a' normal modes; and, secondly, that the normal co-ordinates for the motion of the hydrogen nuclei are parallel to the plane of symmetry of the molecule. Here also the assumptions are reasonable if the equilibrium state is not too strongly bent. To correct in part for the approximations, values of k_Δ are calculated separately from the frequencies $\gamma(CH_2)$ and $\gamma(CD_2)$ by the expression

$$4\pi^2c^2\nu^2 = \frac{k_\Delta}{r_{CO}r_{CH}\cos\theta}\left[\frac{r_{CO}}{r_{CH}\cos\theta}\left(\frac{1}{2m_H} + \frac{1}{m_O}\right) + \frac{2\cos\Delta}{m_O} + \frac{r_{CH}\cos\theta}{r_{CO}}\left(\frac{1}{m_C} + \frac{1}{m_O}\right)\right]; \quad 2\theta = \widehat{HCH}$$

Hence, $k_\Delta(H{\cdot}CHO) = 1{\cdot}24 \times 10^{-12}$ and $k_\Delta(D{\cdot}CDO) = 1{\cdot}02 \times 10^{-12}$ erg rad.$^{-2}$. $\Delta\nu$ was calculated for trial values of Δ by the Wentzel–Kramers–Brillouin equation, as described by Weston.[24] For $\Delta = 27° 30'$ the theoretical and observed splittings are

		H·CHO	D·CDO
$\Delta\nu$ (cm.$^{-1}$)	Calc.	125	68
	Obs.	124	67

Treatment of the k_Δ's as independent parameters implicitly leads to different barrier heights for the normal and dideuterated molecules. The theoretical barriers ($\Delta = 27\frac{1}{2}°$) are

$$V_0(H{\cdot}CHO) = 720\ \text{cm.}^{-1};\ V_0(D{\cdot}CDO) = 590\ \text{cm.}^{-1}$$

The average value, 650 cm.$^{-1}$, represents the extra stability conferred on the excited state by virtue of its non-planarity.

(c) *The rotational constants.* The experimental constants of the 0^+ level of the excited state are consistent with the assumption of a non-planar configuration, but are not sufficiently accurate of themselves to exclude a planar configuration. Four parameters define the geometry of the excited state, the C–H and C–O bond lengths, the $\widehat{HCH}$ interbond

[23] Costain and Sutherland, *J. Phys. Chem.*, 1952, **56**, 321.
[24] Weston, *J. Amer. Chem. Soc.*, 1954, **76**, 2645.

angle, and the angle Δ. For $\Delta = 27\frac{1}{2}°$ satisfactory agreement with the experimental constants is found (Table 11) with $r_{CO} = 1{\cdot}32_2$ Å, $r_{CH} = 1{\cdot}09$ Å, and $\widehat{HCH} = 120°$. The values of Δ and $\widehat{HCH}$ determine $\widehat{HCO} = 116\frac{1}{2}°$. Some mutual adjustment of r_{CH} and either the $\widehat{HCH}$ or the $\widehat{HCO}$ bond angle is certainly possible, but the agreement obtained with [$^2H_1$]formaldehyde is a fairly sensitive indication that the parameters are essentially correct.

TABLE 11. *Rotational constants of excited formaldehyde.*

	Calculated [a]			Observed [b]		
	H·CHO	H·CDO	D·CDO	H·CHO	H·CDO	D·CDO
$A_{[v]}' - D_{[v]}'$	7·835	5·262	3·621	7·85	5·26	3·61
$D_{[v]}'$	1·067	0·959	0·878	1·065 [c]	0·97	0·88
δ	0·0145	—	—	0·0145 [d]	—	—

[a] $r_{CH} = 1{\cdot}09$ Å, $r_{CO} = 1{\cdot}32_2$ Å, $\widehat{HCH} = 120°$, $\widehat{HCO} = 116\frac{1}{2}°$. [b] For the 0^+ excited state level (Section 4). [c] Dyne, ref. 8(*c*). [d] For the 0^- excited state level (Dieke and Kistiakowsky, ref. 3).

(8) *Electronic Configuration of the Excited State.*—The configuration of the electronic ground state of formaldehyde is usually written [25]

$$KK(O, 2s;\ a_1)^2(\sigma_{CH};\ a_1)^2(\sigma_{CH};\ b_1)^2(\sigma_{CO};\ a_1)^2(\pi_{CO};\ b_2)^2(n_O;\ b_1)^2:\ A_1 \quad . \quad (8)$$

the symbol n_O denoting the higher non-bonding orbital, approximately O, $2p$, centred on the oxygen nucleus. The lowest unoccupied orbital of planar formaldehyde is $(\pi^*_{CO};\ b_2)$, the configuration of the first excited state of the C_{2v} molecule being [25]

$$\ldots.(\pi_{CO};\ b_2)^2(n_O;\ b_1)(\pi^*_{CO};\ b_2):\ A_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Higher excited states have been assigned speculatively to the configurations (10) and (11).

$$\ldots.(\pi_{CO};\ b_2)^2(n_O;\ b_1)(\sigma^*_{CO};\ a_1):\ B_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

$$\ldots.(\pi_{CO};\ b_2)(n_O;\ b_1)^2(\pi^*_{CO};\ b_2):\ A_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

At equilibrium, however, the first excited state is not planar. When the molecule bends, the gap between the energies of the π_{CO} and π^*_{CO} orbitals narrows and their contribution to bonding (and antibonding) across the C–O link diminishes. In a strongly bent configuration ($\widehat{HCH} \approx \widehat{HCO} \approx 109°$) these orbitals are equivalent to a pair of non-bonding orbitals, approximately sp^3, one localised on the oxygen nucleus and the other on carbon; the former is more tightly bound and correlates with the π_{CO} orbital of the planar molecule. The A' configurations of the strongly bent molecule are represented in order of increasing energy by (12)—(14), (12) being the (unstable) ground state of pyramidal formaldehyde.

$$\ldots.(n_O;\ a')^2(n_O;\ a'')^2:\ A' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

$$\ldots.(n_O;\ a')(n_O;\ a'')^2(n_C;\ a'):\ A' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

$$\ldots.(n_O;\ a'')^2(n_C;\ a')^2:\ A' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

The lowest A'' state of the bent molecule arises by promotion of an $(n_O;\ a'')$ electron to the $(n_C;\ a')$ orbital (vacant in the C_s ground state). The configuration is

$$\ldots.(n_O;\ a')^2(n_O;\ a'')(n_C;\ a'):\ A'' \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

The correlation with the configurations of C_{2v} formaldehyde is shown in Fig. 6.

The state at 28,250 cm.$^{-1}$ obviously correlates with the $A_2 - A''$ state of Fig. 6. It is, however, not so strongly bent as the hypothetical configuration (15) and is energetically more stable than either (9) or (15). The C–O bond is nominally a five-electron bond, three of the electrons occupying the π_{CO}–n_O and π^*_{CO}–n_O orbitals in which the capacity for bonding and antibonding has been weakened by the change of shape. Approximately, the antibonding electron cancels the bonding power of one of the electrons in the bonding orbital,

[25] McMurry, *J. Chem. Phys.*, 1941, **9**, 231.

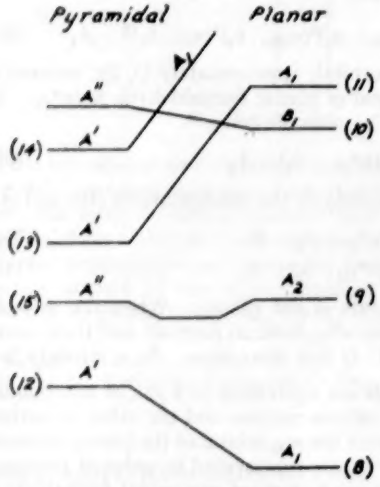
and the C–O bond in excited formaldehyde should, therefore, be weaker and somewhat longer than a 3-electron bond in a planar molecule. The bond length (1·32 Å) fulfils this expectation quite well.

	MeOH	H·CHO *A″*	$CO_3^=$	$H·CO_3^-$
No. of electrons	2	—	2	3
r_{CO} (Å)	1·434 [a]	1·32 [a]	1·31 [b]	1·27 [d]
			1·24—1·26 [c]	1·24—1·26 [c]

[a] Ivash and Dennison, *J. Chem. Phys.*, 1953, **21**, 520. [b] Elliot, *J. Amer. Chem. Soc.*, 1937, **59**, 1380. [c] Brown, Peiser, and Turner-Jones, *Acta Cryst.*, 1949, **2**, 167. [d] Zacharisen, *J. Amer. Chem. Soc.*, 1940, **62**, 1011. [e] Sugawara, Kakado, and Nitta, *X-sen Kondantai*, 1951, **6**, 85.

The factor governing the geometry of the *A″* state is the energy of the singly-occupied π_{CO}–n_O orbital.[10] If the π_{CO} and π^*_{CO} orbitals of the planar molecule uncouple, this orbital falls in energy and becomes increasingly non-bonding; but the uncoupling is not automatically profitable for, although the highest occupied orbital (π^*_{CO} in the planar configuration) is graded down in energy, the remaining orbitals are graded up. In a non-conjugated system, however, the uncoupled form is preferred when the number of

FIG. 6.



The energies of the electronic configurations of C_{2v} formaldehyde are arranged in the order deduced semi-theoretically by McMurry.[25] The position of the higher *A″* electronic configuration of the pyramidal molecule relative to the adjacent *A′* configurations is uncertain.

electrons is sufficient to fill the non-bonding orbitals. [Comparison of –C≡C– (*linear*) with ⁄N=N⁄ and ⁄O–O⁄ (*bent*) directly illustrates the principle of this effect.] In the $A_2 - A''$ configuration of formaldehyde, where the outermost π^*_{CO}–n_O orbital is singly occupied, the energy balance is critical; the result is a compromise in which the high-energy π^*_{CO} orbital of the planar structure is avoided without the hybridisation change to (15) being complete. A possible analogy is with the ground state of nitrogen dioxide ($\widehat{ONO} = 134°$; Moore [26]) or with the $^2A_1$ excited state of NH_2 ($\widehat{HNH} \approx 160°$; Herzberg and Ramsay [27]), both odd-electron molecules. The result is not general, however, and in other cases (*e.g.*, the A_u state of acetylene [28]); the hydridisation change is well defined.

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THE UNIVERSITY, GLASGOW, W.2. [*Received, July 4th*, 1955.]

[26] Moore, *J. Opt. Soc. Amer.*, 1953, **43**, 1045.
[27] Herzberg and Ramsay, *Discuss. Faraday Soc.*, 1953, **14**, 11.
[28] Ingold and King, *J.*, 1953, 2702.

185. *The Stereochemistry of the Tropane Alkaloids. Part VIII.* The Absolute Configurations of the Nitrogen Atoms in Some Optically Active Tropanols and Derived Quaternary Salts.*

By Ödön Kovács, Gábor Fodor, and Miklós Halmos.

Absolute configurations have been assigned to the nitrogen atoms in quaternary salts prepared from (−)-ecgoninol and ethyl iodoacetate, and from (−)-norecgoninol with ethyl iodoacetate and methyl iodide. In the products from the first route the *N*-acetic acid residue is oriented towards the pyrrolidine ring, in those from the second route towards the piperidine ring. These findings are related to results obtained in other series.

The recent observation of the formation of lactone salts from the tertiary bases and ethyl iodoacetate, and of *N*-epimeric ester-ammonium salts from the nor-compounds by reaction with ethyl iodoacetate and subsequent quaternisation with methyl iodide, made possible the assignment of definite configurations to the nitrogen atoms in tropane-3α : 6β-diol, oscine, and derived quaternary salts.

In order further to evaluate the relative importance of the two factors (the Pitzer effect arising from strain in the five-membered ring, and the occurrence of hydrogen-bonding between the unshared electron pair of the nitrogen atom and the hydroxyl group attached to the pyrrolidine ring) which were considered [1] to give rise to this selectivity of quaternisation we have now extended the investigation to ecgoninol (2β-hydroxymethyltropan-3β-ol) and norecgoninol, compounds related to cocaine,[2] to which absolute configurations [3] could be assigned. The availability of optically pure ecgoninol makes it possible to distinguish between optically active *N*-epimers in this group more easily and reliably by measurement of $[\alpha]_D^{20}$ than by m. p.s and crystal photographs.

With ethyl iodoacetate, diacetylecgoninol (I*b*) gave the ester-salt (II*a*) from which were prepared, in the usual way, the betaine (II*b*) and the slightly dextrorotatory carboxymethyl-compound (II*c*). Similarly, there was obtained from norecgoninol (I*d*) [prepared by von Braun degradation of (I*b*)] *N*-ethoxycarbonylmethyl-3β-hydroxy-2β-hydroxymethyl-nortropanium chloride (III*a*). This was converted into the free acid (III*c*), the betaine (III*b*), and the diacetyl ester (III*d*). With methyl iodide in toluene at 120° the free base from (III*d*) gave the lactone salt (IV), together with an amorphous mixture, presumably of partially acetylated isomeric lactones and ester salts. However, upon hydrolysis this mixture furnished only the carboxymethyl compound (V*a*) and the corresponding betaine (V*b*).

The carboxymethyl derivatives and betaines from these two reaction sequences show striking differences in rotational values. Quaternisation of ecgoninol produced a strong positive shift in rotation, whilst the reverse sequence gave compounds in which the original lævorotation was maintained or increased. Although the lactone salt (IV) is an exception to this rule, its reconversion into the strongly lævorotatory (V*a*) and (V*b*) excludes the possibility that racemisation may have occurred during quaternisation. The optical inactivity of the salt (IV) is perhaps not surprising since such bridged tropanes as the cyclic ureide of *N*-carbamoylnorecgonine and the $C_{(2)}$-epimeric tetrahydro-1 : 3-oxazines from the 2-methylnortropan-3-ols show a dextro-shift by comparison with their unbridged parents.[2a] The correlation of conformational changes with rotational values in this field requires closer examination.

The uncertainty as to whether the formula (IV) correctly represents the lactone, or whether the 3-hydroxyl group is involved in lactonisation, does not affect the conclusion that this lactone is derived from *Na*-carboxymethyl-3β-hydroxy-2β-hydroxymethyltropanium iodide (see Part VI [1] for nomenclature), and that identical configurations at the nitrogen can

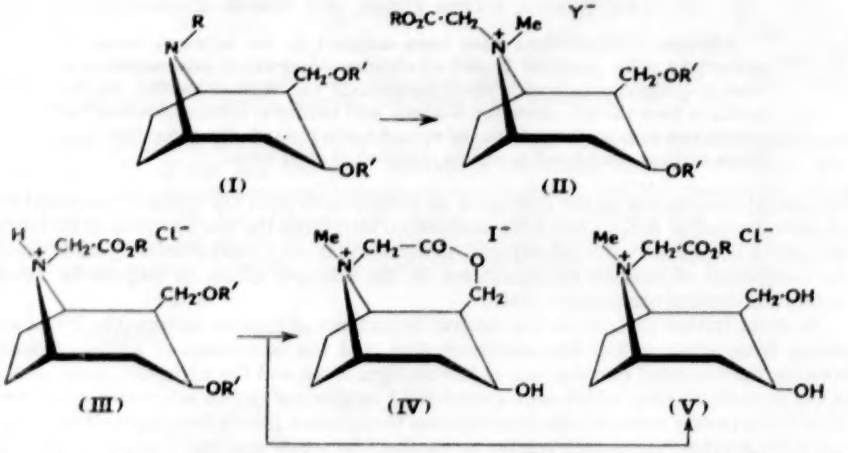
* Part VII, Kovács, Weisz, Zoller, and Fodor, *Helv. Chim. Acta*, 1956, **39**, 99.

[1] Fodor, Tóth, and Vincze, Part VI, *J.*, 1955, 3504.

[2] (*a*) Fodor and Kovács, *J.*, 1953, 724; (*b*) Fodor, Kovács, and Weisz, *Nature*, 1954, **174**, 131.

[3] Hardegger and Ott, *Helv. Chim. Acta*, 1955, **38**, 312.

be deduced for the salts (III) and (V), the opposite configuration occurring in the quaternary salts (II*a*—*c*). Thus the *N*-methyl groups in (I*a*) and (I*b*) and the ethoxycarbonylmethyl group in the *free base* related to (III) appear to be predominantly oriented towards the piperidine ring. These findings thus indicate the predominating importance of the Pitzer



R	R′	$[\alpha]_D^{20}$	R	R′	Y⁻	$[\alpha]_D^{20}$	R	R′	$[\alpha]_D^{20}$	R	R′	Y⁻	$[\alpha]_D^{20}$
Formula (I)			Formula (II)				Formula (III)			Formula (V)			
(*a*) Me	H	−23·3°	Et	Ac	I	−21°	(*a*) Et	H	−42·6°	H	—	Cl	−38·6°
(*b*) Me	Ac	−57	*	H	*	+8·5	(*b*) *‡	H	−64·3	*	—	*	−60·8
(*c*) CN	Ac	−72·4	H	H	Cl	+4·1	(*c*) H	H	−45				
(*d*) H	H	†					(*d*) Et	Ac	−38·4				

* Absent. † No data. ‡ Also no Cl⁻.

effect, for strong hydrogen bonding between hydroxyl and nitrogen in the tertiary bases would orient *N*-substituents in the latter towards the pyrrolidine ring.

Quaternisations of the tropines are now being studied.

Experimental

Unless otherwise stated, rotations were measured in dry MeOH.

3β-*Acetoxy*-2β-*acetoxymethyltropane* (*Diacetylecgoninol*) (I*b*).—The oily residue (59·7 g.) obtained by refluxing ecgoninol hydrochloride [24] (41·5 g.) with acetic anhydride (120 ml.) for ½ hr. and concentrating the solution under reduced pressure was treated with water (200 ml.) and potassium carbonate and extracted with ether (300 ml. in all). Distillation gave the product (48·1 g.), b. p. 155—157°/4 mm., $[\alpha]_D^{20}$ −57·0 ± 1° (*c* 2·105). The base (2·55 g.) in dry acetone (30 ml.), with dry ethanolic hydrogen chloride (2·38 ml. of 15·3%), gave, on addition of dry ether (10 ml.), the *diacetate hydrochloride* (2·7 g.), m. p. 198° (decomp.), $[\alpha]_D^{20}$ −32·8° ± 1° (*c* 1·917) (Found: C, 53·3; H, 7·7; N, 4·9; Cl⁻, 12·2. $C_{13}H_{22}O_4NCl$ requires C, 53·5; H, 7·6; N, 4·8; Cl⁻, 12·2%).

3β-*Acetoxy*-2β-*acetoxymethyl*-N*b*-*ethoxycarbonylmethyltropanium Iodide* (II*a*).—Ecgoninol diacetate (12·27 g.) and ethyl iodoacetate (32·1 g.) were heated in a sealed tube at 70° for 48 hr. The product was washed with chloroform, dried, and recrystallised from dry ethanol–ether, to give the *iodide* (18·9 g.), m. p. 153°, $[\alpha_D^{20}]$ −2·1° ± 1° (*c* 1·888) (Found: C, 43·6; H, 6·2; N, 3·15; I⁻, 27·0. $C_{17}H_{28}O_6NI$ requires C, 43·5; H, 6·0; N, 3·0; I⁻, 27·0%).

3β-*Hydroxy*-N*b*-*carboxymethyl*-2β-*hydroxymethyltropanium Chloride* (II*c*).—A suspension of alkali-free silver oxide (from 3·4 g. of nitrate) in water (100 c.c.) was shaken with the ester iodide (II*a*) (4·68 g.) for 5 min. and then filtered. The filtrate was treated with concentrated hydrochloric acid (50 ml.), boiled for 4 hr., decolorised (charcoal), and evaporated. Recrystallisation of the residue from ethanol–ether gave the *acid chloride* (2·32 g., 87%), m. p. 210°

(decomp.), $[\alpha]_D^{20}$ +4·1° ± 1° (*c* 1·933) (Found: C, 50·1; H, 7·4; N, 5·3; Cl⁻, 13·0. $C_{11}H_{20}O_4NCl$ requires C, 49·7; H, 7·6; N, 5·3; Cl, 13·3%).

Nb-*Carboxymethyl*-3β-*hydroxy*-2β-*hydroxymethyltropanium Betaine* (II*b*).—By the method described below for (V*b*) the above chloride (2·65 g.) and silver oxide provided the *betaine* (2·02 g.), m. p. 272° (decomp.), $[\alpha]_D^{20}$ +8·5° ± 1° (*c* 0·939 in 90% MeOH) (Found: C, 57·7; H, 8·4; N, 6·2. $C_{11}H_{19}O_4N$ requires C, 57·6; N, 8·35; N, 6·1%).

3β-*Acetoxy*-2β-*acetoxymethyl*-N-*cyanonortropane* (I*c*).—Diacetylecgoninol (38·3 g.) in benzene (300 ml.) was added drop by drop during 4 hr. to a vigorously stirred solution (previously dried over calcium chloride) of freshly distilled cyanogen bromide (35 g.) in benzene (350 ml.). The mixture was refluxed for 5 hr. and evaporated to dryness. The yellow crystals (25·65 g.) were washed with ether (2 × 30 ml.) and then extracted with this solvent for 18 hr. Concentration of the combined extract and a further washing gave the *cyano-compound* (24·5 g.), m. p. 109°, $[\alpha]_D^{20}$ −72·4° ± 1° (*c* 2·015) (Found: C, 59·0; H, 6·6; N, 10·4. $C_{13}H_{18}O_4N_2$ requires C, 58·6; H, 6·8; N, 10·5%). From the ethereal mother-liquors diacetylecgoninol (8 g.) was recovered.

3β-*Hydroxy*-2β-*hydroxymethylnortropane* (*Norecgoninol*) (I*d*).—The cyano-compound (36 g.), sodium hydroxide (36 g.), and water (350 ml.) were refluxed for 8 hr. The residue obtained by acidifying (Congo-red) the solution with hydrochloric acid and evaporating it to dryness was extracted with dry ethanol (8 × 100 ml.), and the extract was concentrated to 60 ml. and treated with the calculated quantity of sodium methoxide. Evaporation, extraction with chloroform (200 ml.), and distillation gave the nor-base, b. p. 146—150°/5 mm. The base (0·314 g.) and picric acid (0·460 g.) in ethanol (7 ml.) gave the *picrate* (0·45 g. after recrystallisation from ethanol), m. p. 180° (Found: C, 43·5; H, 4·6; N, 14·7. $C_{14}H_{18}O_9N_4$ requires C, 43·5; H, 4·7; N, 14·5%).

N-*Ethoxycarbonylmethyl*-3β-*hydroxy*-2β-*hydroxymethylnortropanium Chloride* (III*a*).—Crude norecgoninol (19·1 g.), ethyl iodoacetate (12·83 g.), and dry ethanol (90 ml.) were kept at room temperature for 36 hr. The solution in chloroform (150 ml.) of the brownish syrupy residue obtained by evaporating the mixture *in vacuo* was washed with water. The water was extracted with chloroform (50 ml.), and the combined chloroform solutions were dried ($MgSO_4$), acidified with dry alcoholic hydrogen chloride, and evaporated. Crystallised from alcohol–ether the residue gave the *chloride* (12 g.), m. p. 195—196° (decomp.), $[\alpha]_D^{20}$ −42·6° ± 1° (*c* 2·015) (Found: C, 51·8; H, 7·8; N, 5·3; Cl⁻, 12·8. $C_{12}H_{22}O_4NCl$ requires C, 51·7; H, 7·6; N, 5·0; Cl⁻, 12·7%).

N-*Carboxymethyl*-3β-*hydroxy*-2β-*hydroxymethylnortropanium Chloride* (III*c*).—The ester (2·78 g.), water (20 ml.), and concentrated hydrochloric acid (10 ml.) were refluxed 3 hr. and evaporated to dryness. Recrystallisation of the residue from methanol–ether gave the *chloride* (2·22 g.), m. p. 181° (decomp.), $[\alpha]_D^{20}$ −45° ± 1° (*c* 1·997) (Found: C, 47·9; H, 7·4; N, 5·5; Cl⁻, 13·8. $C_{10}H_{18}O_4NCl$ requires C, 47·7; H, 7·2; N, 5·6; Cl⁻, 14·1%).

This specimen, water (20 ml.), and fresh silver oxide (3·4 g.) were shaken for 5 min. Filtration (charcoal) and evaporation *in vacuo* gave the *betaine* (III*b*) (1·95 g.), m. p. 247° (decomp.), $[\alpha]_D^{20}$ −64·3° ± 1° (*c* 0·932) (Found: C, 55·6; H, 7·8; N, 6·5. $C_{10}H_{17}O_4N$ requires C, 55·8; H, 7·8; N, 6·5%), after crystallisation from ethanol–ether.

3β-*Acetoxy*-2β-*acetoxymethyl*-N-*ethoxycarbonylmethylnortropanium Chloride* (III*d*).—The ester-salt (III*a*) (2·78 g.) and acetic anhydride (25 ml.) were heated for 4 hr. on the steam-bath and kept overnight at room temperature. The residue obtained by concentration *in vacuo* was crystallised from dry acetone and dry ether, giving the *diacetyl derivative* (2·69 g.), m. p. 164°, $[\alpha]_D^{20}$ −38·4° ± 1° (*c* 1·971) (Found: C, 52·8; H, 7·3; N, 3·8; Cl⁻, 9·7. $C_{16}H_{26}O_6NCl$ requires C, 52·8; H, 7·2; N, 3·85; Cl⁻, 9·7%).

Na-*Carboxymethyl*-3β-*hydroxy*-2β-*hydroxymethyltropanium Iodide Lactone* (IV).—Ethanolic sodium ethoxide (2·12 ml. of 5·42%) was added to the diacetyl derivative (1·819 g.) in dry acetone (40 ml.). The precipitate was removed at the centrifuge, and the base, freed from acetone, was heated for 10 hr. at 120—125° with toluene (5 ml.) and methyl iodide (4 ml.). The red crystals were collected (the filtrate was retained; see below), washed with acetone, and recrystallised from dry ethanol–ether, giving the *lactone* (0·422 g.), m. p. 200° (decomp.), $[\alpha]_D^{20}$ ±0° (*c* 1·926) (Found: C, 38·7; H, 5·7; N, 3·7; I⁻, 37·4. $C_{11}H_{18}O_3NI$ requires C, 38·95; H, 5·35; N, 3·9; I⁻, 37·4%).

Na-*Carboxymethyl*-3β-*hydroxy*-2β-*hydroxymethyltropanium Chloride* (V*a*).—(*a*) The lactone (0·727 g.), 50% aqueous methanol (30 ml.), freshly precipitated silver chloride (0·43 g.), and water (10 ml.) were shaken for 6 hr. Silver iodide was removed and the solution and concentrated hydrochloric acid (20 ml.) were refluxed for 2 hr., filtered (charcoal), and evaporated *in vacuo*. From dry methanol–ether the residue gave the *chloride* (0·320 g.), m. p. 205°

(decomp.), $[\alpha]_D^{20}$ $-38{\cdot}6° \pm 1°$ (*c* 0·983) (Found: C, 50·0; H, 7·6; N, 5·6; Cl^-, 13·3. $C_{11}H_{20}O_4NCl$ requires C, 49·7; H, 7·6; N, 5·3; Cl^-, 13·35%).

(*b*) The red syrupy residue, from evaporation of the acetone–toluene mother-liquor from (IV), was treated in water (20 ml.) with alkali-free silver oxide (from 1·7 g. of silver nitrate). The residue obtained by filtration, refluxing for 3 hr. with concentrated hydrochloric acid, and evaporation formed from methanol–ether crystals of the chloride (0·795 g.), m. p. 204° alone and mixed with a specimen from (*a*), $[\alpha]_D^{20}$ $-38{\cdot}0° \pm 1°$ (*c* 1·92).

This chloride (0·265 g.), water (5 ml.), and silver oxide (from 0·34 g. of silver nitrate) were shaken for 5 min. Filtration, evaporation to dryness, and recrystallisation from dry methanol–ether gave the *betaine* (V*b*) (0·198 g.), m. p. 238° (decomp.), $[\alpha]_D^{20}$ $-60{\cdot}8° \pm 1°$ (*c* 2·20 in 90% methanol) (Found: C, 58·1; H, 8·2; N, 6·2%).

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186. *Complex Fluorides. Part IV.* The Structural Chemistry of Complex Fluorides of the General Formula* ABF_6.

By B. Cox.

Lattice constants for a large number of complex fluorides of the formula ABF_6 have been determined. The distribution of the $NaSbF_6$, $KSbF_6$, and $BaSiF_6$ structures in this series cannot be accounted for solely by radius-ratio effects.

IN Part I [1] a discussion of the occurrence of the dipotassium hexafluoro-silicate (cubic), -germanate (trigonal), and -manganate (hexagonal) structures among complex fluorides of the formula A_2BF_6 (where A is a large cation) led to the conclusion that the distribution is, to a first approximation, random. In this paper the distribution of the common structures in the complex fluorides of general formula ABF_6 is considered; here A may be a univalent or bivalent cation with B a quinquevalent or quadrivalent element respectively. The results of many new partial structure determinations, together with data by earlier workers, are summarised in Table 1.

We conclude that, as with members of the A_2BF_6 series, the distribution of structures cannot be satisfactorily interpreted solely on the basis of radius-ratio effects. Although most salts of the larger cations crystallise with the trigonal barium hexafluorosilicate structure (co-ordination number round the cation 8), described by Wells [2] as a distorted cæsium chloride-type of structure, and many salts of smaller cations crystallise with the sodium chloride structure (co-ordination number 6), the hexafluorophosphates examined all crystallise with the latter structure. Potassium, rubidium, and cæsium hexafluorophosphates are thus the only members of the series in which potassium, rubidium, and cæsium possess the lower co-ordination number.

It should be noted that the cell side reported for sodium hexafluorophosphate [3] is larger than that found for the silver salt. Comparison of the cell dimensions of the hexafluorophosphates and the corresponding fluorides (Table 2), which have the same structure, suggests that, of these two, the lattice constant of the silver salt is very close to the value which would be expected for it, whereas that of the sodium salt is not. However, Bode's value for the cell constant of sodium hexafluorophosphate has been confirmed and the anomaly in the length of the cell sides of the sodium and silver salts remains unexplained.

* Part III, *J.*, 1954, 3251.

[1] Part I, Cox and Sharpe, *J.*, 1953, 1783.
[2] Wells, "Structural Inorganic Chemistry," 2nd Edition, Oxford, 1950, p. 294.
[3] Table 1, ref. *c*.

TABLE 1. *Structures of* ABF_6 *type.*

Structural type is indicated by: C (CsCl), N (NaCl), or T (trigonal). Values of *a* are followed by α (in parentheses). Anions are in order of increasing size as determined from the cell sides of their trigonal salts.

Anion	Na^+ Ca^{2+}	Ag^+ Sr^{2+}	K^+ Ba^{2+}	Rb^+	Cs^+
SiF_6^{2-}	—	—	T [a] 4·75 (98°)	—	—
GeF_6^{2-}	—	—	T [a] 4·83 (98)	—	—
PF_6^-	N 7·61 [b,c]	N 7·52 [b]	N 7·76 [d] T [d] 4·85 (94)	N 7·92 [b]	N 8·19 [b,d]
TiF_6^{2-}	—	—	T [b,e] 4·87 (98·2)	—	—
RuF_6^{2-}	—	—	T [f,g] 4·87 (98)	—	—
PtF_6^{2-}	—	T [h] 4·74 (97·8°)	T [g,h] 4·88 (98)	—	—
PdF_6^{2-}	—	T [h] 4·72 (98·2)	T [h] 4·88 (98·4)	—	—
AsF_6^-	—	N 7·74 [b]	T [b] 4·92 (97·2)	T [b] 5·00 (97·1°)	T [b] 5·20 (96°)
VF_6^-	—	C 9·52 [b]	T [b,g] 4·92 (97·2)	T [b] 5·01 (97)	T [b] 5·24 (96·2
RuF_6^-	—	—	T [f,g] 4·96 (97·5)	T [f,g] 5·08 (97)	T [f,g] 5·25 (96·2)
SnF_6^{2-}	—	—	T [b,g] 4·97 (96·4)	—	—
SbF_6^-	N 8·18 [i]	C 9·85 [i,j]	C 10·15 [k]	T [i] 5·11 (96·5)	T [i] 5·32 (96·9)
TaF_6^-	N 8·27 [b]	—	C 10·29 [b]	T 5·14 (96·4) [b]	T 5·32 (95·8) [b]
NbF_6^-	N 8·27 [b]	—	C 10·29 [b]	T 5·14 (96·4) [b]	T 5·32 (95·8) [b]

[a] Hoard and Vincent, *J. Amer. Chem. Soc.*, 1940, **62**, 3126. [b] Present work. [c] Bode and Teufer, *Z. anorg. Chem.*, 1952, **268**, 20. [d] Bode and Clausen, *ibid.*, 1951, **265**, 229. [e] Hanawalt, Rinne, and Frevel, *Ind. Eng. Chem. Anal.*, 1938, **10**, 457. [f] Weise and Klemm, *Z. anorg. Chem.*, 1955, **279**, 74. [g] Klemm, *Angew. Chem.*, 1954, **66**, 468. [h] D. W. A. Sharp, personal communication. [i] Schrewelius, *Z. anorg. Chem.*, 1938, **238**, 241. [j] Bode, *ibid.*, 1951, **267**, 62. [k] Bode and Voss, *ibid.*, 1951, **264**, 144. [l] Schrewelius, *Arkiv Kemi*, 1942, *B*, **16**, No. 7.

TABLE 2.

	NaF [m]	AgF [m]	KF [m]	RbF [m]	CsF [m]	$NaPF_6$ [c]	$AgPF_6$ [b]	KPF_6 [b,d]	$RbPF_6$ [b]	$CsPF_6$ [b,d]
a (Å) ...	4·62	4·92	5·34	5·64	6·01	7·61	7·52	7·76	7·92	8·19
Increase	—	0·30	0·42	0·30	0·37	—	Negative	0·24	0·16	0·27

[m] Wyckoff, "Crystal Structures," Interscience, New York, 1951. For other refs. see Table 1.

In view of the interest in the structure of the iodohexafluoride ion,[4] attempts were made to determine the structures of potassium, rubidium, and cæsium iodohexafluorides. A powder photograph which could be indexed on a cubic cell ($a = 11{\cdot}90$ Å) was obtained for the potassium salt; this could not be repeated, however, and similar photographs could not be obtained for the rubidium or cæsium salts.

EXPERIMENTAL

Phosphorus.—Hexafluorophosphates of silver, rubidium, and cæsium were prepared by fluorination of a mixture of the metal, or metal chloride, and excess of phosphoric oxide with bromine trifluoride. Sodium fluorophosphate was prepared by fluorination of sodium metaphosphate (prepared by heating sodium dihydrogen phosphate to 600°) with bromine trifluoride [5] (Found: Ag, 42·1. Calc. for $AgPF_6$: Ag, 42·7. Found: PF_6, 63·0. Calc. for $RbPF_6$: PF_6, 62·9. Found: PF_6, 50·6. Calc. for $CsPF_6$: PF_6, 52·1%).

Arsenic.—Lithium, sodium, potassium, rubidium, cæsium, and silver fluoroarsenates were prepared by fluorination of mixtures of the metal halide, or silver, and arsenic trioxide in 1 : 1 molecular proportions with bromine trifluoride.[6] The powder photograph of sodium fluoroarsenate could not be indexed on a cubic unit cell of the sodium chloride type although it was very similar to those of the other sodium salts. The lithium salt is isomorphous with the sodium salt, but again the photograph could not be indexed (Found: As, 36·1. Calc. for $LiAsF_6$: As, 38·2. Found: As, 34·6. Calc. for $NaAsF_6$: As, 35·3. Found: As, 32·4. Calc. for $KAsF_6$: As, 32·9. Found: As, 26·9. Calc. for $RbAsF_6$: As, 27·3. Found: As, 23·05. Calc. for $CsAsF_6$: As, 23·25. Found: Ag, 35·9. Calc. for $AgAsF_6$: Ag, 36·4%).

Vanadium.—Sodium, potassium, rubidium, cæsium, and silver hexafluorovanadates(v) were prepared by fluorination of mixtures of the metal halide, or silver, and vanadium trichloride in

[4] Sharpe, *Quart. Rev.*, 1950, **4**, 115.
[5] Emeléus and Woolf, *J.*, 1950, 164.
[6] Woolf and Emeléus, *J.*, 1949, 2865.

1 : 1 molecular proportions with bromine trifluoride.[7] The vanadium trichloride was prepared essentially by Emeléus and Gutmann's modification [7] of Ruff and Lickfett's method.[8] Sodium hexafluorovanadate was not isomorphous with sodium hexafluoroantimonate, but was isomorphous with lithium and sodium fluoroarsenates (Found: V, 26·8. Calc. for $NaVF_6$: V, 27·1. Found: V, 25·4. Calc. for KVF_6: V, 25·0. Found: V, 21·4. Calc. for $RbVF_6$: V, 20·4. Found: V, 16·9. Calc. for $CsVF_6$: V, 17·1%).

Antimony.—The powder photograph of a sample of lithium fluoroantimonate prepared by Woolf [6] showed this compound to be isomorphous with lithium and sodium fluoroarsenates.

Tantalum.—Fluorotantalates of lithium, sodium, potassium, rubidium, and cæsium were prepared by Gutmann and Emeléus's method.[9] The powder photograph of lithium fluorotantalate showed it to be isomorphous and isodimensional with lithium fluoroniobate; the lines could not be indexed, however, and the photograph was not similar to those of the other series of isomorphous lithium and sodium salts whose photographs could not be indexed (Found: Ta, 60·5. Calc. for $LiTaF_6$: Ta, 59·5. Found: Ta, 58·1. Calc. for $NaTaF_6$: Ta, 57·0. Found: Ta, 54·9. Calc. for $KTaF_6$: Ta, 54·4. Found: Ta, 48·7. Calc. for $RbTaF_6$: Ta, 47·6. Found: Ta, 42·5. Calc. for $CsTaF_6$: Ta, 42·3%).

Niobium.—Lithium, sodium, potassium, rubidium, and cæsium fluoroniobates were prepared by Gutmann and Emeléus's method.[9] The powder photograph of lithium fluoroniobate showed it to be isomorphous and isodimensional with lithium fluorotantalate, but no further interpretation was possible (Found: Nb, 43·0. Calc. for $LiNbF_6$: Nb, 43·4. Found: Nb, 39·9. Calc. for $NaNbF_6$: Nb, 40·4. Found: Nb, 38·0. Calc. for $KNbF_6$: Nb, 37·8. Found: Nb, 31·7. Calc. for $RbNbF_6$: Nb, 31·8. Found: Nb, 27·2. Calc. for $CsNbF_6$: Nb, 27·3%).

Titanium.—Barium fluorotitanate was prepared by fluorination of a 1 : 1 mixture of barium chloride and titanium dioxide with bromine trifluoride. Attempts to prepare the calcium and the strontium salt by a similar method resulted in products whose powder photographs bore no resemblance to those of any of the known ABF_6 type structures.

Tin.—Barium fluorostannate was prepared from stannic chloride and barium chloride in 1 : 1 molecular proportions by fluorination with bromine trifluoride. Attempts to prepare the calcium and the strontium salt and to determine their structures were unsuccessful.

Iodine.—Iodohexafluorides were prepared by Aynsley, Nichols, and Robinson's method.[10]

X-Ray powder photographs were taken and interpreted as described in Part II.[11]

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University Chemical Laboratory, Cambridge. [*Received, October 7th,* 1955.]

[7] Emeléus and Gutmann, *J.*, 1949, 2979.
[8] Ruff and Lickfett, *Ber.*, 1911, **44**, 506.
[9] Gutmann and Emeléus, *J.*, 1950, 1046.
[10] Aynsley, Nichols, and Robinson, *J.*, 1953, 623.
[11] Part II, Cox and Sharpe, *J.*, 1954, 1798.

187. *The Retardation of Benzaldehyde Autoxidation. Part VII.* Further Studies of the Actions of Polycyclic Aromatic Hydrocarbons.*

By A. H. Turner and William A. Waters.

The work of Part VI * has been continued; kinetic results obtained with substituted anthracenes, 1 : 2-benzanthracenes, and other polycyclic aromatic hydrocarbons are reported and are reviewed critically. Too many anomalous results have now been obtained for it still to be possible to maintain the view that a numerically simple connection can be traced between the retarding power of a polycyclic aromatic compound and its maximum free valence number, $F_{max.}$, or between retarding power and carcinogenic action, without detailed knowledge of (*a*) the precise reaction mechanism and (*b*) the chemical natures of the reaction products.

Perylene is outstanding in being a strong retarder which has no carbon centre of high $F_{max.}$ whilst 9-methyl-1 : 2-benzanthracene, 9 : 10-dimethylanthracene, and 9 : 10-dimethyl-1 : 2-benzanthracene are exceptional in having scarcely any retarding action.

No simple connections can be traced between the induction period during which a compound retards benzaldehyde autoxidation and its chemical structure. For anthracene it has been established that all the hydrocarbon has been destroyed at the end of the induction period, but that its oxidation products comprise a complex mixture, including anthraquinone, dianthron-9-yl and dianthron-9-ylidene. It is therefore concluded that the retardation of benzaldehyde autoxidation by anthracene involves the consecutive addition of two $Ph{\cdot}CO{\cdot}O_2{\cdot}$ radicals to the *meso*-positions of anthracene or else the dimerisation of the primary single-radical adduct.

In Part VI of this series [1] it was shown that anthracene and 1 : 2-5 : 6-dibenzanthracene acted as retarders of the benzoyl peroxide-catalysed autoxidation of benzaldehyde by combining with benzoylperoxy-radicals, $Ph{\cdot}CO{\cdot}O{\cdot}O$. For a number of other polycyclic aromatic hydrocarbons which were presumed to act in a similar manner it was found that their relative efficiencies as retarding agents could be correlated fairly satisfactorily with the "free valence numbers" of their centres of highest reactivity. Some hydrocarbons, such as anthracene (termed type A), ceased completely to be inhibitors after a time, others, such as 1 : 2-benzanthracene and 3 : 4-benzopyrene (termed type B), which included all the carcinogenic hydrocarbons that had then been tested, became, after a period, weaker but still evident retarders. It was tentatively suggested that the compounds of type B gave quinonoid oxidation products which still had some chain-stopping potency. A few of the hydrocarbons tested, such as chrysene (termed type C), were initially feeble autoxidation retarders, but became more effective as their oxidation products were formed.

Several further aromatic hydrocarbons, and a number of their substitution products, have now been examined in a similar way. In addition, a more detailed study has been made of the reactions which are involved when anthracene is added to autoxidising benzaldehyde. The following sections review critically the conclusions that may be drawn from this experimental evidence.

Efficiencies as Retarding Agents.—Tables 1—3 give the initial rates of oxygen uptake at 60° for systems containing equimolecular amounts of the various compounds tested in solution in 10 ml. of benzaldehyde containing 1·500 g. of benzoic acid and 0·150 g. of benzoyl peroxide as catalyst. Series I contain retarder equivalent to 5 mg. of anthracene, series II retarder equivalent to 10 mg., and series III that equivalent to 15 mg. The classification of reaction types as A, B, or C follows the system given above.

These collected results show that the earlier surmise that there might be a simple connection between the actions of aromatic molecules in retarding autoxidation and their carcinogenic potencies was based upon far too few observations. The highly carcinogenic

* Part VI, *J.*, 1954, 580.

[1] Dunn, Waters, and Roitt, *J.*, 1954, 580.

TABLE 1. *Retardation of the autoxidation of benzaldehyde by anthracene and acridine derivatives: initial rates of the oxidation at 60°.*

Anthracene deriv.	Ml. of O_2 per min. for 10 ml. of Ph·CHO I	II	III	Anthracene deriv.	Ml. of O_2 per min. for 10 ml. of Ph·CHO I	II	III
Unsubst.	(D) 0·12	0·059	v.s.	9 : 10-Diallyl-	—	(0·40)	—
9-Methyl-	(D) 0·38	0·12	(D) 0·13	9 : 10-Dichloro	—	(1·5)	—
9-Ethyl-	—	0·22	—	9 : 10-Dichloromethyl-	—	(0·68)	—
9-Phenyl-	0·12	0·058	v.s.	9 : 10-Diacetoxy-	—	v.l.	—
9-Cyano-	—	0·11	—	9 : 10-Dibenzoyloxy-	—	v.l.	—
9-Bromo-	—	0·14	—	9-Ethyl-10-methyl-	—	(0·45)	—
9-Methoxy-	—	0·15	—	9-Benzoyloxy-10-methyl	—	v.l.	—
9-Benzoyloxy-	—	0·14	—				
Anthrone	—	(0·8)	—	Acridine deriv.			
9 : 10-Dimethyl-	—	(v.l.)	—	Unsubst.	0·195	0·074	v.s.
9 : 10-Diethyl-	—	(0·31)	—	5-Methyl-	—	0·43	—
9 : 10-Diphenyl-	(3·35)	0·84	0·30	5-Phenyl-	—	0·46	—

v.l. = very large rate; v.s. = very small rate.

For figures in parentheses the rate was increasing during the period of measurement, but has been extrapolated to zero time.

Results marked (D) are due to Dr. J. R. Dunn and are quoted from Part VI.

TABLE 2. *Retardation of the autoxidation of benzaldehyde by 1 : 2-benzanthracene derivatives: initial rates of the oxidation at 60°.*

Compound	Ml. of O_2 per min. for 10 ml. of Ph·CHO I	II	III
1 : 2-Benzanthracene	(D) 1·04	0·42	0·19
3-Methyl-1 : 2-benzanthracene	0·27	0·17	v.s.
4-Methyl- ,,	1·17	0·34	—
5-Methyl- ,,	(D) 0·93	0·33	0·12
7-Methyl- ,,	—	0·096	—
9-Methyl- ,,	16·8	14·7	10·0
10-Methyl- ,,	(D) 1·31	0·42	0·22
10-*iso*Propyl- ,,	(D) 6·73	1·39	0·83
5-Pentyl- ,,	0·98	0·30	0·072
5 : 6-*cyclo*Pentano- ,,	(D) 0·45	0·15	0·097
9 : 10-Dimethyl- ,,	—	(v.l.)	—
9 : 10-Diphenyl- ,,	2·49	0·97	—
Cholanthrene	—	0·10	—
20-Methylcholanthrene	(D) 0·37	0·098	0·061

All benzanthracene derivatives give autoxidation curves of type B.

See also footnotes to Table 1.

hydrocarbon 9 : 10-dimethyl-1 : 2-benzanthracene, for instance, has scarcely any retarding action and resembles 9 : 10-dimethylanthracene. Again perylene, which is not carcinogenic, is a very potent inhibitor of autoxidation.

The correlation, *i.e.*, log R varies as $F_{max.}$, between initial retarding efficiency, R calculated as $1/\{n(-d[O_2]/dt - 0{\cdot}002)\}$, and free valence number, $F_{max.}$, that was applied in Part VI, was previously noted as failing for pyrene; it is now seen to fail markedly also for perylene which has a relatively low free valence number, and for stilbene which has no retarding action. Nevertheless Fig. 1*A* indicates that the overall concordance of this relationship, originally due to Kooyman and Farenhorst,[2] is surprisingly good considering the approximations and assumptions that are inherent in the underlying theory. Critical inspection of the plot shows, however, that most of the consistency is found for molecules of the anthracene type for which a common reaction process, *i.e.*, addition to a *meso*-position, is presumably involved. For molecules of other shapes the correlation is poor and the criticism that support for the general relation depends mainly on artificially selected data cannot wholly be refuted. It may now be suggested that correlations of this type between structural calculations and experimental measurements of chemical reactivities hold only for groups of reactions that have exactly the same mechanism.

[2] Kooyman and Farenhorst, *Trans. Faraday Soc.*, 1953, **49**, 58.

TABLE 3. *Retardation of the autoxidation of benzaldehyde by other polycyclic hydrocarbons: initial rates of the oxidation at 60°.*

Compound		Class	Ml. of O_2 per min. per 10 ml. of Ph·CHO I	II	III
Naphthacene		A	—	0·056	—
Chrysene	(D)	C	10·8	6·35	4·84
Pyrene	(D)	C	0·44	0·23	0·14
3 : 4-Benzopyrene	(D)	B	0·16	0·081	0·051
Picene		C	11·7	5·22	3·07
Perylene		B	0·08	0·02	v.s.
Stilbene				No inhibiting power	
Fluorene				No inhibiting power	
Fluoranthene		C	—	7·72	—
Acenaphthene		?C	1·78	1·26	—
1-Methylnaphthalene				No inhibiting power	
1 : 2-3 : 4-Dibenzanthracene		B	2·36	1·02	0·56
1 : 2-5 : 6-Dibenzanthracene	(D)	B	1·82	0·79	0·55
1 : 2-7 : 8-Dibenzanthracene	(D)	B	1·30	0·58	0·35
3′-Methyl-1 : 2-7 : 8-dibenzanthracene		B	0·98	0·32	0·18
3′-Methyl-1 : 2-5 : 6-dibenzanthracene	(D)	B	1·22	0·50	0·26
2-Methyl-3 : 4-benzophenanthrene	(D)	C	8·44	3·84	2·84
6-Methyl-3 : 4-benzophenanthrene		C	—	2·60	—
7-Methyl-3 : 4-benzophenanthrene		C	—	3·10	—
1 : 2-3 : 4-Dibenzophenanthrene	(D)	C	13·3	5·37	3·39
1 : 2-5 : 6-Dibenzophenanthrene		C	6·12	4·07	2·93
9-Benzoyloxy-1 : 2-5 : 6-dibenzanthracene		?	—	3·57	—
5-Benzoyloxy-3 : 4-benzopyrene		B	—	0·079	—
Benzanthrone				No inhibiting power	

See footnotes to Table 1.

TABLE 4. *Connections between the autoxidation-retarding powers (R) of aromatic hydrocarbons and calculated structural factors.*

$R = 1/\{n(-d[O_2]/dt - 0{\cdot}002)\}$. $F_{max.}$ = maximum free valence.
E^* = Singlet–triplet state excitation frequency (in cm.$^{-1}$).

Hydrocarbon	n	$F_{max.}$	$-d[O_2]/dt$	$\log_{10} R$	E^*
3 : 4-Benzopyrene	1	0·212	0·081	1·092	—
Anthracene	2	0·202	0·059	0·928	14,850 [a]
1 : 2-Benzanthracene	1	0·196	0·42	0·377	16,500 [b]
3-, 4-, 5-, 7-, and 10-Methylbenzanthracene	1	—	0·1—0·4	0·4—0·7	16,250—17,000 [b]
9-Methylbenzanthracene	1	—	14·7	−1·17	16,260 [b]
1 : 2-5 : 6-Dibenzanthracene	2	0·180	0·79	−0·20	18,300 [c]
1 : 2-7 : 8-Dibenzanthracene	1	0·192	0·58	0·236	—
Pyrene	4	0·151	0·23	0·045	16,800 [d]
Chrysene	2	0·139	6·35	1·10	19,800 [d]
Phenanthrene	4	0·134	v.l.	− 2?	21,600 [d]
2-Methyl-3 : 4-benzophenanthrene	3?	—	3·84	−0·11	19,700 [b]
Naphthacene	4	0·212	0·056	0·65	10,250 [e]
1 : 2-3 : 4-Dibenzanthracene	2	0·181	1·02	−0·31	—
Picene	2	0·139	5·22	−1·02	—
Perylene	4	0·156	0·02	1·10	—
Stilbene	2	0·163	v.l.	−3?	21,700 [d]
Fluoranthene	2	0·152	7·72	−1·19	—
Acridine	1	—	0·074	1·14	—

$F_{max.}$ values are from sources cited by Kooyman and Farenhorst.[e]
[a] McGlynn, Pudhye, and Kasha, *J. Chem. Phys.*, 1955, **23**, 593. [b] Moodit and Reid, *ibid.*, 1954, **22**, 252. [c] McClure, *ibid.*, 1951, **19**, 670. [d] *Idem*, *ibid.*, 1949, **17**, 905. [e] Kooyman and Farenhorst, *Trans. Faraday Soc.*, 1953, **49**, 58.

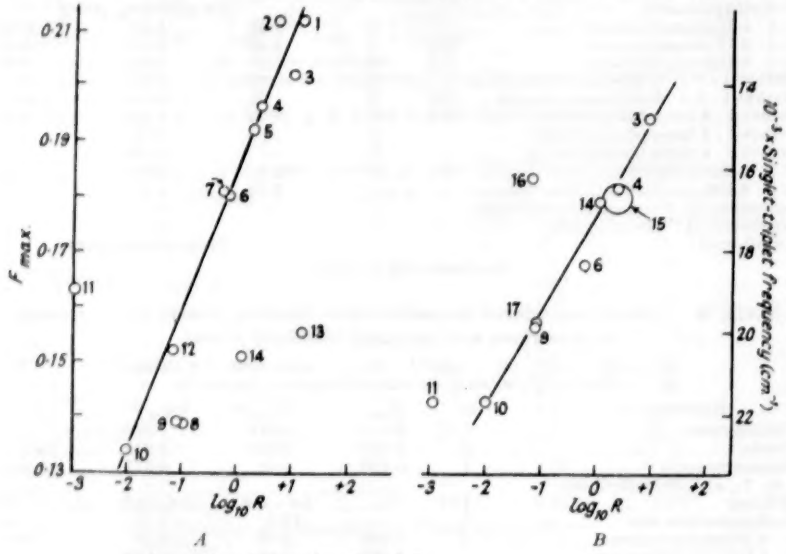
Szwarc [3] and Levy and Szwarc [4] suggested that a more appropriate correlation may be that between the free-radical reactivity of a hydrocarbon and the energy required for its photochemical excitation to its lowest triplet state, since the latter presumably has the structure of a chemically reactive diradical form.[5] Fig. 1*B* shows that this correlation is somewhat more satisfactory than the correlation with maximum free valence number.

[3] Szwarc, *J. Chem. Phys.*, 1955, **23**, 204.
[4] Levy and Szwarc, *J. Amer. Chem. Soc.*, 1955, **77**, 1949.
[5] Lewis and Kasha, *ibid.*, 1944, **66**, 2100; Lewis and Calvin, *ibid.*, 1945, **67**, 1232.

It may be noted (Table 1) that acridine is a slightly poorer inhibitor than anthracene, though it has been suggested by Dewar [6] that it should be slightly more reactive to free-radical attack, just as pyridine is slightly more reactive than benzene.[7] The result accords with the finding by Levy and Szwarc [4] that acridine reacts with methyl radicals less easily than does anthracene.

Effects of substituents on the initial retarding actions of anthracene are shown in Table 1. Except for phenyl substitution the replacement of one *meso*-hydrogen atom of anthracene by any other group approximately halves the initial retarding power: with two substituents the retarding power becomes negligible, except again for the diphenyl derivative. In Table 5 the efficiencies of 9-substituted anthracenes as retarders of

FIG. 1. *Connections between retarding powers of hydrocarbons and theoretical factors.*



A, *Connections between* log *R* *and* $F_{max.}$.
B, *Connections between* log *R* *and singlet–triplet excitation energy.*

Key:

1 = 3 : 4-Benzopyrene.	2 = Naphthacene.	3 = Anthracene.
4 = 1 : 2-Benzanthracene.	5 = 1 : 2-7 : 8-Dibenzanthracene.	6 = 1 : 2-5 : 6-Dibenzanthracene.
7 = 1 : 2-3 : 4-Dibenzanthracene.	8 = Picene.	9 = Chrysene.
10 = Phenanthrene.	11 = *trans*-Stilbene.	12 = Fluoranthene.
13 = Perylene.	14 = Pyrene.	
15 = 3-, 4-, 5-, and 10-Methyl-1 : 2-benzanthracenes (large circle).		
16 = 9-Methyl-1 : 2-benzanthracene.	17 = Methylbenzophenanthrenes.	

benzaldehyde autoxidation are compared with their reactivities towards the 2-cyano-2-propyl free radical, as determined by Kooyman and Farenhorst.[8] Neither series of figures can be correlated with either the polar or the electromeric properties of the substituents.

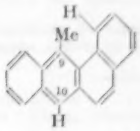
With the substituted 1 : 2-benzanthracenes (Table 2) noticeable changes in reactivity occur only when alkyl groups occupy *meso*-positions. The effect of a methyl group in the reactive, sterically unhindered 10-position is similar to that of a methyl group in a single *meso*-position in anthracene, but substitution of a methyl in the sterically blocked 9-position (see I) is even more effective than methylation in both the 9- and the 10-position in destroying the antioxidant power of the aromatic molecule.

[6] Dewar, *ibid.*, 1952, **74**, 3361.
[7] Hey and Williams, *Discuss. Faraday Soc.*, 1953, **14**, 219; *J. Chem. Phys.*, 1955, **23**, 757.
[8] Kooyman and Farenhorst, *Nature*, 1955, **175**, 1949.

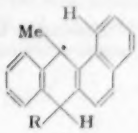
TABLE 5. *Reactivities of 9-substituted anthracene derivatives.*

	Relative rate constant for reaction with $Me_2C(CN)\cdot$ radicals at 55°	Reciprocal of initial rate of O_2 uptake in Ph·CHO at 60° (calc. on the basis of anthracene = 2·0
Anthracene	2·00	2·00
9-Methylanthracene	2·12	0·98
9-Ethylanthracene	1·54	0·54
9-Phenylanthracene	—	1·9
9-Methoxyanthracene	2·15	0·79
9-Cyanoanthracene	1·30	1·07
9-Bromoanthracene	1·39	0·84
9 : 10-Dimethylanthracene	0·24	Very small
9 : 10-Diphenylanthracene	—	0·14

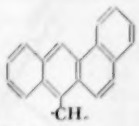
One tentative explanation of this marked positional effect is that the radical (II) from 9-methylbenzanthracene has its point of free valence so encumbered that it cannot take part in any further radical combinations but tends to dissociate back to the molecule (I) and the chain-propagating $Ph\cdot CO\cdot O_2\cdot$ radical.



(I)



(II)



(III)

The low retarding efficiencies of the *meso*-dimethylanthracenes and benzanthracenes may perhaps be due to the concurrent action of chain-transfer processes such as :

$$Ph\cdot CO\cdot\ (Ph\cdot CO\cdot O_2\cdot) + H\cdot CH_2\cdot Anth \longrightarrow Ph\cdot CO\cdot H\ (Ph\cdot CO\cdot O_2H) + CH_2\cdot Anth$$

$$\cdot CH_2\cdot Anth + O_2 \longrightarrow \cdot O_2CH_2\cdot Anth \text{ etc.}$$

since radicals, $\cdot CH_2\cdot$Anth, such as (III), are extended resonance systems which undoubtedly can be formed with great ease.[9] The marked difference between methyl and phenyl substitution could be explained in this way. However no satisfactory interpretation of all the present results can be offered.

Induction Periods and Oxidation Products.—All the anthracene derivatives tested belong to group A (see p. 879), and the benzanthracene and dibenzanthracene derivatives to group B giving eventual oxygen uptake rates of 10—20 times their initial values. As indicated in Part VI this final oxidation rate seems to be somewhat related to the redox

TABLE 6.

Hydrocarbon	Redox potential (v) of quinone	Final rate of O_2 uptake of Ph·CHO (ml./min.)
Anthracene	0·150	Very large
1 : 2-Benzanthracene	0·224	8·2
5-Methyl-1 : 2-benzanthracene	0·168	8·0
3-Methyl-1 : 2-benzanthracene	0·208	6·57
7-Methyl-1 : 2-benzanthracene	0·209	5·55
1 : 2-5 : 6-Dibenzanthracene	0·255	5·1
1 : 2-7 : 8-Dibenzanthracene	0·238	4·1

potential of the corresponding *meso*-quinone (Table 6). Since for several of these compounds the duration of the " induction period " of markedly retarded autoxidation of the benzaldehyde is proportional to the amount of the material that has been added, it is reasonable to suggest that the induction period, measured by extrapolating to zero oxygen uptake the time of onset of fast oxidation, indicates the time taken to destroy all the initial retarder. This conclusion has been confirmed quantitatively in the case of anthracene by measuring fluorimetrically its change of concentration in the autoxidising system and showing (see Fig. 2) that the time required for its complete disappearance coincides with the time at which the retardation of the oxidation of benzaldehyde ceases.

[9] Beckwith and Waters, *J.*, 1956, in the press.

Fig. 2 shows also that the rate of removal of the anthracene is a zero-order process. This is to be expected since in all the autoxidation mixtures benzoyl peroxide has been added in a constant large excess to act as the chain-starting catalyst. Since for the chain oxidation of benzaldehyde there should be a general relation (Rate of chain starting) = (Rate of chain termination), *i.e.*, $-d[Anth]/dt = +d[Ph{\cdot}CO{\cdot}O{\cdot}]/dt$, it might be expected that equimolar quantities of different hydrocarbons would give identical, or numerically

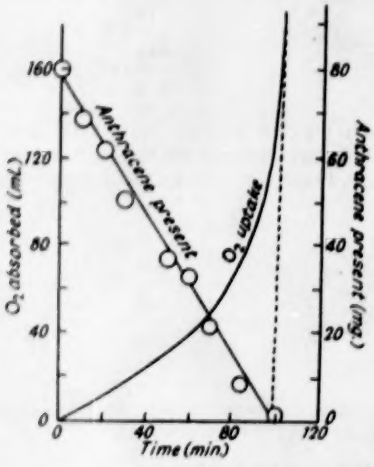


FIG. 2. *Retardation of benzaldehyde autoxidation by anthracene at 60°.*

Connection between disappearance of anthracene (fluorimetric determinations) and the rate of oxygen uptake.

related, induction periods according to whether the aromatic compound was effective in stopping 1, 2, or more reaction chains. Tables 7 and 8 show that not only is this far from being the case, but also that the product (Initial oxygen uptake rate) × (Induction period) is not constant, as might happen if all the oxygen absorbed during the period of retarded autoxidation were used, as $Ph{\cdot}CO{\cdot}O_2{\cdot}$, to destroy the polycyclic compound. Differences are marked even between closely related hydrocarbons; and the anomalous substances 9 : 10-dimethylanthracene, 9-methyl-1 : 2-benzanthracene, and 9 : 10-dimethyl-1 : 2-benzanthracene, exhibit very small induction periods except when added in very high concentration.

Even the rate of destruction of anthracene is larger than was expected. From Fig. 2

TABLE 7. *Induction periods for the retardation of benzaldehyde autoxidation by anthracene derivatives.*

Anthracene deriv.		Induction period (min.) I	II	III	Ind. period (II) × init. rate
Unsubst.		56	119	174	7
9-Methyl-	(D)	14·5	24·2	35·5	2·9
9-Ethyl-		—	25	—	5·5
9-Phenyl-		74	130	—	7·6
9-Cyano-		—	170	—	—
9-Bromo-		—	100	—	14·0
9-Methoxy-		—	33	—	5·0
9-Benzoyloxy-		—	76·5	—	10·7
Anthrone		—	59·5	—	48
9 : 10-Dimethyl-		—	7	—	v.l.
9 : 10-Diethyl-		—	15	—	(5)
9 : 10-Diphenyl-		13	36	65	30
9 : 10-Diallyl-		—	19	—	(8)
9 : 10-Dichloro-		—	(7)	—	—
9 : 10-Bischloromethyl-		—	24	—	(20)
9 : 10-Diacetoxy-		—	v.s.	—	—
9 : 10-Dibenzoyloxy-		—	v.s.	—	—

See footnotes to Table 1.

it can be seen that 10 mg. are consumed at 60° in about 100 min., when 0·150 g. of benzoyl peroxide catalyst is used. This corresponds to a rate of $5{\cdot}6 \times 10^{-7}$ mole/min. and from the data of Table 9 the activation energy of the measured reaction, which should be that of the formation of active radicals from the benzoyl peroxide, is 27·7 kcal. mole^{-1}. Bawn and Mellish,[10] who used the rate of destruction of the free radical *NN*-diphenyl-*N'*-picrylhydrazyl in a number of solvents to measure the rate of radical formation from benzoyl peroxide, give 29·6 kcal. mole^{-1} as the activation energy, and from their data it would be expected that the induction period for the 10 mg. of anthracene would be about 7 times what we found. However, other investigators have given higher values for the rate of decomposition of benzoyl peroxide, which depends to some extent on the polarity of the solvent and often is accelerated by a chain reaction involving solvent molecules.[11] Again, the efficiency of *NN*-diphenyl-*N'*-picrylhydrazyl as a radical collector has been doubted.[12]

Some of the oxidation of the anthracene may be due to the heterolytic action [13] of the perbenzoic acid formed, though Bäckström and Beatty [14] concluded that autoxidising

TABLE 8. *Induction periods for the retardation of benzaldehyde autoxidation by higher hydrocarbons.*

Hydrocarbon		Induction periods (min.) I	II	III	Ind. period (II) × init. rate
1 : 2-Benzanthracene	(D)	27	56·5	99	23·8
3-Methyl-1 : 2-benzanthracene		36	78·5	141	13·4
4-Methyl- ,,		34	71·5	—	24·3
5-Methyl- ,,	(D)	27·5	50	100	16·5
5-Pentyl- ,,		26	51	95	15·5
7-Methyl- ,,		—	73	—	7·0
9-Methyl- ,,		v.s.	v.s.	v.s.	—
10-Methyl- ,,	(D)	16·5	29·3	40	12
9 : 10-Dimethyl- ,,		?	?	v.s.	—
9 : 10-Diphenyl- ,,		24	43	79	41·8
Cholanthrene		79·5	109	—	11·0
20-Methylcholanthrene	(D)	33	68	120	6·7
1 : 2-3 : 4-Dibenzanthracene		14·5	35	49·5	36
1 : 2-5 : 6-Dibenzanthracene	(D)	34	71	105	56
1 : 2-7 : 8-Dibenzanthracene	(D)	47	108	205	63
3'-Methyl-1 : 2-5 : 6-dibenzanthracene	(D)	36	82	117	42
3'-Methyl-1 : 2-7 : 8-dibenzanthracene		49	128	160	42
10-*iso*Propyl-1 : 2-benzanthracene	(D)	7·3	15	23·5	20·9
5 : 6-*cyclo*Pentano-1 : 2-benzanthracene	(D)	21	56	90	8·4
3 : 4-Benzopyrene	(D)	52	115	165	9·3
Naphthacene		—	10·5	—	0·59
1 : 2-Benzonaphthacene		—	19·2	—	—

See footnotes to Table 1. Results marked (D) have not been reported previously.

TABLE 9. *Inhibition of benzaldehyde autoxidation by anthracene.*

Temp.	Initial rate of O_2 uptake (ml./min.)	Ind. period (min.) (extrap.)	Temp.	Initial rate of O_2 uptake (ml./min.)	Ind. period (min.) (extrap.)
60·0°	0·056	91	70·0°	0·25	26
62·4	0·069	66	72·5	0·37	21
65·0	0·12	52	75·0	0·51	15
67·5	0·15	39			

Measurements were made with 0·0100 g. of anthracene in 10 ml. of benzaldehyde containing 1·500 g. of benzoic acid and 0·150 g. of benzoyl peroxide (Series II of Tables 1 and 7).

benzaldehyde destroys anthracene at least 600 times more quickly than does perbenzoic acid; and with many of the other hydrocarbons destruction by the autoxidising system is undoubtedly much more rapid than destruction by the per-acid.

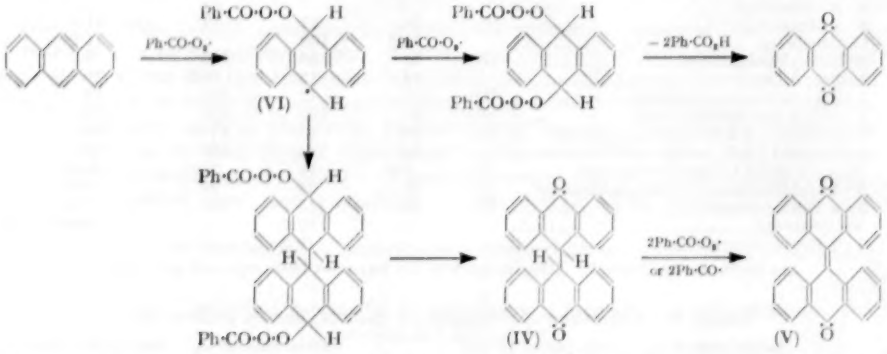
[10] Bawn and Mellish, *Trans. Faraday Soc.*, 1951, **47**, 1216.
[11] Tobolsky and Mesrobian, "Organic Peroxides," Interscience Publ. Inc., New York, 1954, pp. 72—88.
[12] Russell and Tobolsky, *J. Amer. Chem. Soc.*, 1954, **76**, 396; Hammond, Sen, and Boozer, *ibid.*, 1955, **77**, 3246; Walling, *J. Polymer Sci.*, 1954, **14**, 395.
[13] Roitt and Waters, *J.*, 1949, 3060.
[14] Bäckström and Beatty, *J. Phys. Chem.*, 1931, **55**, 2530.

To obtain further experimental evidence concerning the mode of destruction of anthracene the products resulting from its autoxidation in the presence of both oxygen and benzoyl peroxide have been investigated. From air-blown benzaldehyde not containing added catalyst or inhibitor there has been isolated a trace of *s*-diphenylethylene dibenzoate $(Ph{\cdot}CO{\cdot}O{\cdot}CHPh{\cdot})_2$, which is also formed by the direct reaction of benzaldehyde with benzoyl peroxide or *tert.*-butyl peroxide [15] and is probably one of the chain-ending products of the unretarded autoxidation of benzaldehyde. In the presence of anthracene this substance does not appear to be formed. When the autoxidation is prolonged until the destruction of the anthracene is complete a dark tar is produced in which, besides anthraquinone, dianthron-9-yl (IV) and dianthon-9-ylidene (V) have been identified by their colour reactions and infrared spectra. The last product was also isolated in an experiment where only 60% of the anthracene had been destroyed; but in neither case could a quantitative separation of oxidation products be achieved.

The formation of the dianthronyl (IV) was suspected by Bäckström and Beatty,[14] who isolated a 90% yield of anthraquinone at room temperature but noted that this yield diminished as the temperature was raised.

The mechanism of oxidation of anthracene in benzaldehyde can now be extended to the scheme shown. Products (IV) and (V) evidently arise by reactions following dimerisation of the initial adduct (VI), the structure of which was indicated by the kinetic studies of Part VI. The formation of the dimeric products (IV) and (V) shows that the combination of anthracene with benzoylperoxy-radicals is a two-stage addition entirely analogous to its reactions with 2-cyano-2-propyl radicals [16] and with methyl radicals.[9]

Preliminary studies with 1 : 2-5 : 6-dibenzanthracene have given a still more complex mixture of oxidation products, containing some of the *meso*-dibenzanthraquinone, but there is no evidence, as yet, of any initial homolytic oxidation of either anthracene or



dibenzanthracene at the positions in the side rings which are concerned in their biochemical oxidations.[17]

Evidently the products of the reactions of polycyclic aromatic hydrocarbons with the radicals formed in autoxidising benzaldehyde exhibit all the complexities associated with other homolytic reactions of aromatic compounds, and thus it is not surprising that the values of induction periods listed in Tables 7 and 8 show no simple consistency. Indeed it is remarkable that connections between reactivity and chemical structure can be traced as simply as Fig. 1 indicates. The hope that a broad survey of the effects of polycyclic hydrocarbons in retarding autoxidation might provide a guide to the possible behaviour of carcinogenic substances in biochemical metabolic processes has not been fulfilled, and it now must be recognised that the complexity of homolytic reactions *in vitro*, like those of biochemical reactions *in vivo*, are such that detailed studies of particular hydrocarbons are

[15] Rust, Seubold, and Vaughan, *J. Amer. Chem. Soc.*, 1948, **70**, 3258.
[16] Bickel and Kooyman *Rec. Trav. chim.*, 1952, **71**, 1137; Engelsma, Farenhorst, and Kooyman, *ibid.*, 1954, **73**, 878.
[17] See *Biochem. Soc. Symp.*, 1950, No. 5.

now needed rather than further attempts to derive analogies from considerations of structural formulæ alone.

Experimental

The kinetic measurements of oxygen uptake were carried out by the procedure described [1] in Part VI. Periodic tests of the retarding effect of pure anthracene were made to ensure that each batch of benzaldehyde had been purified to the state that reproducible data could be obtained.

The 1 : 2-benzanthracene, dibenzanthracene, and benzophenanthrene derivatives examined were pure specimens from the Chester Beatty Research Institute and were mainly compounds which had been prepared by Professor J. W. Cook, F.R.S. In view of its unexpected behaviour the sample of 9-methyl-1 : 2-benzanthracene was carefully examined. It still had m. p. 139° [picrate, m. p. 114—115° (decomp.)], as described originally,[18] and its ultraviolet spectrum corresponded exactly to that reported.[19] This spectrum shows a certain degree of blurring of the fine structure characteristic of the 1 : 2-benzanthracene system, which may indicate that the molecule is slightly strained. The anthracene derivatives were synthesised. 9-Methylanthracene, prepared from anthrone,[20] was purified through alumina and had m. p. 79·5—80°. The direct dimethylation of anthracene [21] gave very poor yields of 9 : 10-dimethylanthracene but the following procedure was far more satisfactory. 9-Methylanthracene was formylated with *N*-methylformanilide, and the resulting 10-methyl-9-anthraldehyde, m. p. 161—164°, was heated with 90% hydrazine hydrate and potassium hydroxide in ethylene glycol for 4½ hr. The product was converted into the picrate (purple leaflets, m. p. 170°) which was decomposed by passing its benzene solution through alumina. The pure 9 : 10-dimethylanthracene crystallised from benzene in yellow needles, m. p. 177·5—178·5°. Perylene was prepared by heating to dull red heat a mixture of di-β-naphthol, phosphorus pentachloride, and phosphoric acid as described by Brass and Tengler; [22] after crystallisation from benzene the yellow sublimate had m. p. 253°; from this was prepared the picrate, m. p. 224—226° (decomp.) (from benzene), and thence, by decomposition with aqueous ammonia, pure perylene, yellow plates, m. p. 263°. The main, more soluble, product of the pyrolysis gave a dark red picrate, m. p. 158°, and proved to be 1 : 1′-dinaphthyl-2 : 2′-ylene oxide, m. p. 152—153°; this was the only product obtained by heating dinaphthol with zinc dust and zinc chloride.[23] Other syntheses followed, and confirmed, accounts in the literature.

Isolation of Products from Benzaldehyde Autoxidations. Products from Anthracene.—Air was blown through a warm solution of anthracene in benzaldehyde (500 ml.) containing a little benzoyl peroxide until the material became pasty owing to separation of benzoic acid. The product was washed repeatedly with sodium hydrogen sulphite solution to remove benzaldehyde, and then with sodium hydrogen carbonate solution to remove benzoic acid. There remained a black tar which in part dissolved in benzene, leaving a residue of anthraquinone. By repeated crystallisation and chromatography of the solution there were also separated a light brown solid, m. p. 240—245°, and a yellowish-green solid, m. p. >360°. The latter crystallised from acetophenone in bright yellow needles and gave an intense cherry-red colour with concentrated sulphuric acid. The product of lower m. p. dissolved in warm alcoholic sodium hydroxide to a red solution, gave faint colours with alcoholic ferric chloride and diazotised *p*-nitroaniline, and was easily oxidised to the product of higher m. p. (dianthron-9-ylidene) by chloranil in hot nitrobenzene or *tert.*-butyl peroxide in tetrachloroethane. Treatment with acetic anhydride in hot pyridine gave 10 : 10′-diacetoxy-9 : 9-dianthryl. Both substances were synthesised by the method of Barnett and Matthews [24] and their identities confirmed by comparisons of infrared spectra.

From another oxidation mixture which had been aërated for a shorter period, 52% of unchanged anthracene was recovered together with 32% of anthraquinone and 2·5% of dianthronylidene, but no dianthronyl. From an air-blown sample of benzaldehyde to which

[18] Cook, Robinson, and Goulden, *J.*, 1937, 393.
[19] Jones, *J. Amer. Chem. Soc.*, 1940, **62**, 148.
[20] Sieglitz and Marx, *Ber.*, 1923, **56**, 1619.
[21] Badger, Goulden, and Warren, *J.*, 1941, 18.
[22] Brass and Tengler, *Ber.*, 1931, **64**, 1648.
[23] Marschalk, *Bull. Soc. chim. France*, 1928, **43**, 1388; Lundin, *J. Gen. Chem.* (*U.S.S.R.*), 1939, **9**, 682; *Chem. Abs.*, 1940, **34**, 414.
[24] Barnett and Matthews, *J.*, 1923, 380.

neither anthracene nor benzaldehyde had been added there was isolated 0·002% of *s*-diphenylethylene dibenzoate, m. p. 246°, identical with a specimen prepared from benzaldehyde and *tert.*-butyl peroxide.[15]

Determination of Anthracene in Autoxidation Mixtures.—For recovery of anthracene, oxidations were carried out with mixtures of 0·080 g. of hydrocarbon, 1·200 g. of benzoyl peroxide, and 12·0 g. of benzoic acid in 80 ml. of benzaldehyde, which had approximately the same induction period at 60° as the mixtures of Series II of Tables 1 and 7. At 10 min. intervals the autoxidation was arrested and 1·0 ml. samples of the solution were withdrawn, diluted with 100 ml. of purified xylene, and shaken with 100 ml. of concentrated aqueous sodium hydrogen sulphite. After two further sulphite extractions the xylene solutions were treated with 50 ml. of a solution of sodium dithionite (3%) in aqueous potassium hydroxide (4%) and heated at 100° under nitrogen for an hour. After removal of quinones in this way the xylene solution was dried (Na_2SO_4) and then 2 ml. samples were diluted with 25 ml. of fresh xylene, and their fluorescence was measured by using a Hilger " Spekker " fluorimeter which had been calibrated with solutions obtained by serial dilution of a standard containing 0·128 g. of anthracene per l. in xylene. All the anthracene solutions were stored in the dark to prevent loss of hydrocarbon through photo-oxidation. Provided that the instrument was recalibrated regularly reproducible results were obtained.

We thank the Council of the British Empire Cancer Campaign for financial support during 1953—1955, for the completion of this investigation. We are again indebted to members of the Chester Beatty Research Institute, and to colleagues, for help in providing specimens of many of the compounds which we have examined.

The Dyson Perrins Laboratory, Oxford. [*Received, September 19th,* 1955.]

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188. *The Oxidation of Derivatives of o-Phenylenediamine. Part I. Isomeric Phenazine Pigments obtained by Oxidation of 2-Aminodiphenylamine Hydrochloride.*

By Vincent C. Barry, J. G. Belton, J. F. O'Sullivan, and Dermot Twomey.

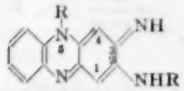
2-Aminodiphenylamine hydrochloride has been oxidised by *p*-benzoquinone. The crude oxidation product, after purification on alumina, yielded the known 2-anilino-3 : 5-dihydro-3-imino-5-phenylphenazine (anilino-*apo*safranine) accompanied by a similar pigment which is shown to be the isomer, 2-amino-3 : 5-dihydro-5-phenyl-3-phenyliminophenazine.

It has been shown in these laboratories that ferric chloride oxidation of mono-substituted *N*-derivatives of *o*-phenylenediamine produces in good yields 2 : 5-substituted derivatives of 3 : 5-dihydro-3-iminophenazine. In this way anilino*apo*safranine (I; R = Ph) was obtained from 2-aminodiphenylamine hydrochloride.[1,2,3] These 2 : 5-substituted derivatives exhibit antituberculosis activity *in vitro* [1] and in mice,[4] and anilino*apo*safranine has been claimed to exert a curative effect in lepromatous leprosy.[5] It has now been shown that the crude ferric chloride oxidation product of 2-aminodiphenylamine hydrochloride contains, as well as anilino*apo*safranine (I; R = Ph), about 5—10% of an isomeric pigment for which the structure (II; R = Ph) is proposed.

The early literature on the ferric chloride oxidation of 2-aminodiphenylamine has been surveyed by Barry and Belton.[2] According to Fischer and Dischinger [6] the main product of the reaction was (I; R = Ph). Kehrmann and Messinger,[7] however, maintained that the main oxidation product had the structure (II; R = Ph). Degradative experiments

[1] Barry, Belton, Conalty, and Twomey, *Nature*, 1948, **162**, 622.
[2] Barry and Belton, *Proc. Roy. Irish Acad.*, 1953, **55**, *B*, 149.
[3] Barry, Belton, Chambers, Conalty, Kelly, and Twomey, *ibid.*, p. 157.
[4] Barry, *Irish J. Med. Sci.*, 1951, 453.
[5] Allday and Barnes, *ibid.*, 1952, 421.
[6] Fischer and Dischinger, *Ber.*, 1896, **29**, 1602.
[7] Kehrmann and Messinger, *J. prakt. Chem.*, 1892, **46**, 568.

on the oxidation product carried out by Fischer and Heiler [8] which are discussed below finally convinced Kehrmann that (I; R = Ph) correctly represented the structure of anilino*apo*safranine. In the present paper it is shown that, when *p*-benzoquinone is used as oxidant in place of ferric chloride, 2-aminodiphenylamine hydrochloride yields as well as the *apo*safranine (I; R = Ph) an approximately equal amount of a second pigment which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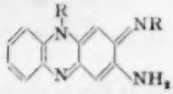
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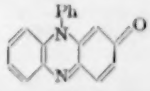

(III)

closely resembles it in properties. Evidence is presented which confirms the structure of anilino*apo*safranine and establishes that the second product is correctly represented by (II; R = Ph) and is identical with the product obtained in small amount by ferric chloride oxidation.

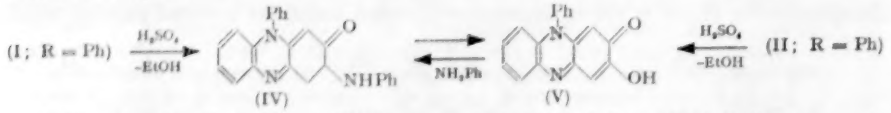
When an aqueous solution of *p*-benzoquinone is added with stirring to an aqueous solution of 2-aminodiphenylamine hydrochloride, a dark red powder separates, which consists for the most part of a mixture of the hydrochlorides of the two phenazines (I and II; R = Ph). The filtrate contains a number of other highly coloured materials only one of which (III) (*apo*safranone [9]) has so far been identified. The crude precipitate was recrystallised from alcohol, the hydrochloride of anilino*apo*safranine (I; R = Ph) for the most part remaining in solution; the crystalline hydrochloride of the isomer (II; R = Ph), which separated in an impure condition, was converted into the base which was purified by chromatography and then formed a dark red crystalline powder, m. p. 257—259°. The more soluble hydrochloride, recovered from the alcohol, was converted into the base and similarly purified, giving bright red crystals, m. p. 203—204°, identical with the anilino*apo*safranine (I; R = Ph) obtained in the ferric chloride oxidation.[2] The high-melting base (II; R = Ph) retains benzene tenaciously and was only obtained solvent-free after 10 hours' heating at 105° under reduced pressure. Like anilino*apo*safranine (I; R = Ph) it then gave analyses correct for $C_{24}H_{18}N_4$ and showed light-absorption maxima at 230, 272, and 455 mμ compared with 280 and 480 mμ for the former. The isomers may be readily distinguished by their different behaviour towards concentrated sulphuric acid and acetic anhydride. Anilino*apo*safranine (I; R = Ph) dissolves in sulphuric acid to a brown-red solution while the isomer forms a green-brown solution, and both solutions become fuchsin-red on dilution. On being warmed with acetic anhydride, the compound (I; R = Ph) forms a red-brown solution which blackens quickly, while the isomer gives a stable reddish-purple solution from which a crystalline monoacetyl derivative separates on cooling.

Molecular-weight determinations on the isomer (II; R = Ph) were not satisfactory, because of its relatively low solubility. The oxidative condensation was therefore effected with *N-cyclo*hexyl-*o*-phenylenediamine. In this case, whether ferric chloride or *p*-benzoquinone was used as oxidising agent, the only product identified appeared from its behaviour with sulphuric acid and acetic anhydride to have structure (II; R = *cyclo*hexyl). This compound was much more soluble than its phenyl analogue and molecular-weight determinations confirmed that we were dealing with a simple structure such as (II).

In agreement with Fischer and Heiler,[8] heating anilino*apo*safranine (I; R = Ph) in a sealed tube with alcoholic sulphuric acid gave a mixture of decomposition products from which anilino*apo*safranone (IV) and hydroxy*apo*safranone (V) were isolated. Similar treatment of the isomer (II; R = Ph) yielded, surprisingly, the same degradation products. It is clear that the anilino*apo*safranone (IV) could not result as a direct degradative product from a compound (II; R = Ph) but it could possibly be formed as a reversion product from the hydroxy*apo*safranone (V) and the liberated aniline; and this was shown to be correct by heating the hydroxy-ketone (V) with aniline and dilute sulphuric acid in alcohol in a sealed tube, anilino*apo*safranone (IV) being obtained in 50% yield. It was

[8] Fischer and Heiler, *Ber.*, 1893, **26**, 378.
[9] Kehrmann and Bürgin, *Ber.*, 1896, **29**, 1819.

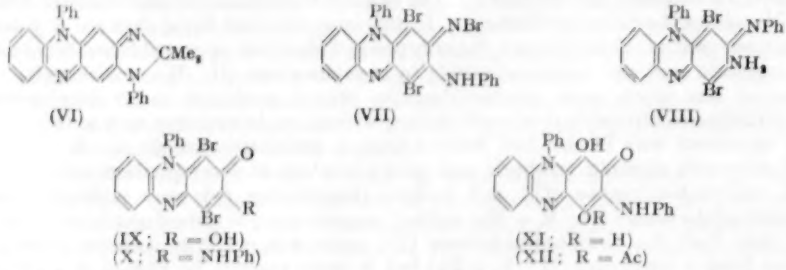
thus clear that these degradations did not provide certain evidence by which the structure (I; R = Ph) for anilino*apo*safranine could be established, and could as readily be adduced in favour of structure (II; R = Ph). Further examination of the isomeric pigments was therefore desirable.



Anilino*apo*safranine reacts readily in warm alcohol with 1-fluoro-2 : 4-dinitrobenzene to form highly insoluble glistening black needles, while with its isomer no reaction takes place under reflux except in the presence of anhydrous sodium acetate. The presence of an aromatic amino-group in the high-melting product is suggested by its behaviour on diazotisation and on treatment with nitrosobenzene. With sodium nitrite and dilute hydrochloric acid under the usual conditions, followed by boiling with alcohol, it gave an insoluble blue powder which has not been identified. A similar product was obtained on treatment in hypophosphorous acid solution with sodium nitrite and subsequent boiling. Again, the high-melting isomer with nitrosobenzene in alcohol slowly yielded a dark green crystalline powder which has not so far been identified. In contrast to this behaviour, anilino*apo*safranine was recovered for the most part unchanged from the diazotisation and the treatment with nitrosobenzene. Although not completely satisfactory these reactions are in agreement with the presence of an NH_2-group in the high-melting isomer.

Furthermore, if the *p*-benzoquinone oxidation of 2-aminodiphenylamine hydrochloride is effected in aqueous acetone, an orange-yellow crystalline base (VI) can be isolated, which shows a striking green-yellow fluorescence in solution. This is confirmed by the isolation of the same product (VI) when anilino*apo*safranine is warmed with acetone in acid solution. Similar glyoxalinophenazines have been made by using other ketones, and show a yellowish-green fluorescence in solution; they will be discussed in a later paper. In contrast with this behaviour of anilino*apo*safranine, treatment of the high-melting isomer with acetone in acid solution leads to products of low solubility in organic solvents and the solutions are not fluorescent. Here again the evidence supports formula (I; R = Ph) for anilino*apo*safranine and formula (II; R = Ph) for the high-melting isomer.

Again, the isomers (I and II; R = Ph) react in carbon tetrachloride solution with bromine or *N*-bromosuccinimide to give tribromo- and dibromo-derivatives, respectively. These are represented by (VII) and (VIII), two bromine atoms presumably entering the *ortho*-positions to the quinonoid system and in (VII) the third bromine atom replaces the imino-hydrogen. If these formulations are correct, then sealed-tube degradations of both bromo-compounds might be expected to give the identical dibromo-hydroxy*apo*safranone (IX) or anilino-dibromo*apo*safranone (X), a bromine atom being lost only from



(VII). [In one case, the anilino-compound (X) would be a reversion product formed as indicated above.] Unexpectedly all the bromine was eliminated from both the bromo-compounds, which each gave the anilinodihydroxy*apo*safranone (XI). This was converted into a monoacetyl derivative, which probably has the structure (XII) as it might be expected that hydrogen bonding would prevent the acylation of the hydroxyl group *ortho*

to the carbonyl group. The formation of the substance (XI) is readily understandable on the basis of the structures (I and II; R = Ph) for the isomeric phenazine pigments.

It should be emphasised that if 2-aminodiphenylamine base is oxidised by *p*-benzoquinone, a mixture of coloured products is obtained which is quite different from that got from the hydrochloride.

Experimental

Oxidation of 2-Aminodiphenylamine Hydrochloride.—(a) *With ferric chloride.* The amine hydrochloride (7·0 g.) in water (350 c.c.) was stirred for 1 hr. with aqueous ferric chloride (16·0 g. in 160 c.c.). The precipitate was dried (6·5 g.) and converted into the base with alcoholic sodium hydroxide. One-half of the dry product in benzene was chromatographed on alumina (Merck). Elution with benzene gave (i) a few crystals which showed a pink fluorescence in benzene, (ii) dark red crystals (0·3 g.; m. p. 257—259°), and (iii) bright red crystals (1·8 g.; m. p. 203—204°). A number of highly coloured bands remained on the column but were not further investigated. Fraction (ii), **2-*amino*-3 : 5-*dihydro*-5-*phenyl*-3-*phenyliminophenazine*** (II; R = Ph), was recrystallised from benzene without change in m. p. (Found: C, 80·8; H, 5·2; N, 13·9. $C_{24}H_{18}N_4,\frac{1}{2}C_6H_6$ requires C, 81·0; H, 5·2; N, 14·0%). After drying at 105°/10 mm. for 10 hr., there was no change in m. p. (Found: C, 79·6; H, 5·1; N, 15·0. $C_{24}H_{18}N_4$ requires C, 79·6; H, 5·0; N, 15·5%). The compound is insoluble in water, slightly soluble in ether, sparingly soluble in alcohol. Fraction (iii) was recrystallised from benzene (Found: C, 79·1; H, 4·9; N, 15·3%) and was **2-anilino-3 : 5-dihydro-3-imino-5-phenylphenazine** (I; R = Ph).

(b) *With* p-*benzoquinone.* The amine hydrochloride (11·0 g.) in hot water (300 c.c.) was stirred at 60° with *p*-benzoquinone (8·0 g.) in water (250 c.c.). The mixture was kept for 2 hr. and the precipitate dried (8·9 g.). Recrystallisation from alcohol gave a hydrochloride (4·4 g.) which was converted into the base and purified chromatographically. The m. p. and mixed m. p. proved its identity with the product (II; R = Ph) above. The alcoholic mother-liquor gave with sodium hydroxide a second base (4·0 g.), which was purified chromatographically. The main product in this fraction was anilino*apo*safranine (I; R = Ph).

Isolation of **2 : 10-*dihydro*-2-*oxo*-10-*phenylphenazine*** (apo*safranone*). The filtrate from the previous preparation, after the separation of the above crude hydrochloride [prepn. (*b*)], when made alkaline with sodium hydroxide, gave a dark finely divided precipitate which was separated by centrifuging. The yield of crude material was very small and a number of filtrates from different preparations were combined. The dried product dissolved to the extent of 25% in benzene, leaving a black powder which was discarded. The benzene extract was chromatographed and gave as main product brown needles of *apo*safranone, m. p. 248—249° (yield <1%), identical with a sample prepared by the method of Kehrmann and Bürgin [9] (after chromatographic purification).

Derivatives of **2-*Amino*-3 : 5-*dihydro*-5-*phenyl*-3-*phenyliminophenazine***.—(i) The base was refluxed in alcohol with 1-fluoro-2 : 4-dinitrobenzene in the presence of anhydrous sodium acetate for 4 hr. The dark precipitate was washed with water and recrystallised from dioxan; the **2 : 4-*dinitrophenyl derivative*** then formed dark green crystals, m. p. 270—272° after drying (3½ hr. at 105° under reduced pressure) (Found: C, 65·4; H, 4·1; N, 15·2. $C_{30}H_{20}O_4N_6,H_2O$ requires C, 65·9; H, 4·0; N, 15·4%). (ii) The base was refluxed for 10 min. with excess of acetic anhydride and cooled. The precipitated ***acetyl derivative*** was washed with light petroleum and recrystallised from benzene; it was a brown powder, m. p. 310° (decomp.) (Found: C, 77·4; H, 5·3; N, 13·9. $C_{26}H_{20}ON_4$ requires C, 77·2; H, 4·95; N, 13·9%). (iii) The base in benzene was refluxed for ½ hr. with excess of methyl sulphate. The deposited ***methosulphate*** recrystallised from alcohol as grass-green needles, m. p. 302—304° (decomp.) (Found: C, 63·3; H, 4·9; N, 11·6; S, 6·7. $C_{26}H_{24}O_4N_4S$ requires C, 63·9; H, 4·9; N, 11·5; S, 6·6%). (iv) Addition of concentrated hydrochloric acid to an alcoholic solution of the base gave the ***salt*** as green shimmering needles, m. p. >350° (Found: C, 69·6; H, 5·5; N, 13·3; Cl, 8·5. $C_{24}H_{18}N_4,HCl,H_2O$ requires C, 69·1; H, 5·0; N, 13·4; Cl, 8·5%).

2-*Amino*-5-cyclo*hexyl*-3-cyclo*hexylimino*-3 : 5-*dihydrophenazine*.—(a) ***Ferric chloride oxidation.*** *N-cyclo*Hexyl-*o*-phenylenediamine hydrochloride (7·7 g.) in alcohol (40 c.c.) and water (200 c.c.) was stirred with ferric chloride solution (34·0 g. in 180 c.c.). The precipitate (6·0 g.) was converted into the base, and recrystallised from benzene as an orange-red powder, m. p. 216—218° (Found: C, 77·4; H, 8·3; N, 14·4. $C_{24}H_{30}N_4,\frac{1}{2}C_6H_6$ requires C, 77·8; H, 8·0; N, 14·2%). This *phenazine* has also been obtained with m. p. 224—226°. No other product was isolated from this oxidation.

(b) ***p-Benzoquinone oxidation.*** The amine hydrochloride (7·5 g.) in 20% aqueous alcohol

(230 c.c.) was stirred for 2 hr. with a warm solution of *p*-benzoquinone (6·0 g. in 240 c.c. of water). The precipitate was converted into the base by alcoholic sodium hydroxide and recrystallised from benzene. It (4·6 g.) was proved by its m. p. and mixed m. p. to be identical with the compound got by the ferric chloride oxidation [*M* (cryoscopically in benzene), 385. $C_{24}H_{20}N_4$ requires *M*, 374].

Sealed-tube Degradations.—(a) *Anilinoaposafranine.* The base (5·0 g.) with 10% sulphuric acid (10 c.c.) and alcohol (10 c.c.) was heated in a sealed tube at 180° for 4 hr. The mixture was then boiled with 10% aqueous sodium hydroxide. A benzene extract of the residue was chromatographed on alumina (Merck). The main band yielded dark-red glistening needles, m. p. 258—260° (decomp.) (about 50 mg.), which were dried at 105°/10 mm. for 10 hr. [Found : C, 78·9; H, 4·8; N, 11·3. Calc. for $C_{24}H_{17}ON_3$ (anilino*apo*safranone) : C, 79·3; H, 4·7; N, 11·5%]. The alkaline filtrate was acidified with acetic acid, giving an orange-yellow flocculent precipitate which recrystallised from alcohol as orange-red needles, m. p. 280° (decomp.) (20 mg.) [Found : C, 74·1; H, 4·3; N, 9·6. Calc. for $C_{18}H_{12}O_2N_2$ (hydroxy*apo*safranone) : C, 75·0; H, 4·2; N, 9·7%]. The methyl ether, prepared according to Fischer and Hepp's method,[11] agreed with their description of hydroxy*apo*safranone methyl ether.

(b) *2-Amino-3 : 5-dihydro-5-phenyl-3-phenyliminophenazine.* The degradation, carried out as above, gave anilino- and hydroxy-*apo*safranone in approximately the same yields.

*Condensation of Aniline with Hydroxy*apo*safranone.*—Hydroxy*apo*safranone (150 mg.), synthesised by Kehrmann's method,[10] was heated with alcohol (10 c.c.), aniline (1 c.c.), and 10% sulphuric acid (5 c.c.) at 180—200° for 3½ hr. Anilino*apo*safranone (75 mg.) was isolated.

Diazotisation of 2-Amino-3 : 5-dihydro-5-phenyl-3-phenyliminophenazine.—(a) *With hypophosphorous acid.* The base (1 g.) in hypophosphorous acid (32%; 70 c.c.) was cooled to 0° and sodium nitrite (0·3 g.) added, the temperature being kept below 5°. The mixture was stirred for 4 hr. and allowed to reach room temperature. The solid product was refluxed with alcoholic ammonia, leaving undissolved a blue powder (0·6 g.) which did not melt and was insoluble in all organic solvents.

(b) *With hydrochloric acid.* This diazotisation was carried out in alcoholic solution by the standard method. Again the main product was a blue powder apparently identical with that got as in (*a*). It was recovered unchanged by addition of water to its solution in concentrated sulphuric acid (Found : C, 68·8; H, 3·6; N, 14·2%).

Attempted diazotisation of anilino*apo*safranine by these methods gave unchanged material.

Bromination of the Isomeric Pigments.—(a) *Of anilino*apo*safranine.* The base (2·8 g.) in carbon tetrachloride (300 c.c.) was stirred with bromine (2 c.c.) in the same solvent (50 c.c.). The precipitated hydrobromide was converted into the 1 : 4 : N³-*tribromo-base* with alcoholic sodium hydroxide and recrystallised from benzene–light petroleum. It was a red powder, m. p. >360° (Found, after being heated for 4 hr. at 105°/10 mm. : Br, 35·9. $C_{24}H_{15}N_4Br_3,C_6H_6$ requires Br, 35·5%). Identical material was obtained when anilino*apo*safranine was heated under reflux in chloroform with *N*-bromosuccinimide.

(b) *Of 2-amino-3 : 5-dihydro-5-phenyl-3-phenyliminophenazine.* The base (0·5 g.) was treated in chloroform (100 c.c.) with bromine (0·5 c.c.) in chloroform. The precipitate was treated with alcoholic sodium hydroxide and the recovered 1 : 4-*dibromo-base* recrystallised from benzene as dark red needles, m. p. 242—244° (Found : Br, 28·8. $C_{24}H_{16}N_4Br_2,\frac{1}{2}C_6H_6$ requires Br, 28·6%). The same material was got when *N*-bromosuccinimide was heated in chloroform with the base.

Sealed-tube Degradation of the Bromo-derivatives.—Parallel experiments were conducted with the two bromo-derivatives. The hydrobromide of the bromo-compound (5 g.) was heated (4 hr.) in a sealed-tube with alcohol (10 c.c.) and 10% sulphuric acid (10 c.c.) at 180°. The mixture was then boiled with 10% aqueous sodium hydroxide (200 c.c.). The filtrate gave on acidification with acetic acid a reddish-yellow precipitate which was purified by repeated dissolution in alkali and reprecipitation with acetic acid. After recrystallisation from alcohol it was got as brown-red crystals (50 mg.) (Found : C, 73·5; H, 4·2; Br, 0. $C_{24}H_{17}O_3N_3$ requires C, 72·9; H, 4·3%). A few mg. of this *2-anilino-3 : 5-dihydro-1 : 4-dihydroxy-3-oxo-5-phenylphenazine* were heated with acetic anhydride and a little pyridine. The product, recovered by dilution with water and recrystallised from methanol, formed brown-red needles, m. p. 230° (Found : Ac, 10·5. $C_{24}H_{16}O_3N_3{\cdot}CO{\cdot}CH_3$ requires Ac, 9·8%). Further treatment failed to raise the acetyl content above this figure.

5 : 2′-Dihydro-2′ : 2′-dimethyl-5 : 1′-diphenylglyoxalino(5′ : 4′-2 : 3)phenazine (VI).—(a) *Oxidation*

[10] Kehrmann, *Ber.*, 1895, **28**, 1709.
[11] Fischer and Hepp, *Ber.*, 1896, **29**, 365.

of 2-aminodiphenylamine hydrochloride in aqueous acetone. The amine hydrochloride (4 g.) in 50% aqueous acetone (60 c.c.) was treated with hot aqueous *p*-benzoquinone (4 g. in 150 c.c.). The solution was made alkaline with sodium hydroxide, and the precipitate dried (3·8 g.) and extracted with boiling benzene, leaving a residue (0·8 g.). The extract was chromatographed on alumina (Merck). The main product, the *glyoxalinophenazine*, which was the first one eluted, showed a yellow-green fluorescence. It was obtained as orange yellow needles (2 g.), m. p. 236—237° (Found : C, 81·3; H, 6·2; N, 12·7. $C_{27}H_{22}N_4,\frac{1}{2}C_6H_6$ requires C, 81·8; H, 5·7; N, 12·7%) and retained benzene after 12 hours' heating at 105°/10 mm. The same material is obtained when ferric chloride is used in place of *p*-benzoquinone.

(b) *Condensation of acetone and anilino*apo*safranine.* The base (1 g.) in acetone (50 c.c.) containing syrupy phosphoric acid (10 c.c.) was heated on the water-bath for 15 min. The mixture was made alkaline and the separated solid dried and extracted with boiling benzene. On chromatography the same fluorescing material (m. p. and mixed m. p.) was obtained (0·2 g.).

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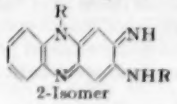
189. *The Oxidation of Derivatives of o-Phenylenediamine. Part II.* Phenazine Pigments obtained from N-Alkyl-, N-cycloAlkyl-, N-Alkylphenyl-, and N-Alkoxyphenyl-o-phenylenediamine Hydrochloride.*

By VINCENT C. BARRY, J. G. BELTON, J. F. O'SULLIVAN, and DERMOT TWOMEY.

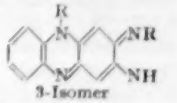
Various *N*-substituted derivatives of *o*-phenylenediamine hydrochloride have been oxidised with ferric chloride and *p*-benzoquinone and the highly coloured phenazine pigments related to 2-anilino-3 : 5-dihydro-3-imino-5-phenylphenazine (anilino*apo*safranine) and its isomer, 2-amino-3 : 5-dihydro-5-phenyl-3-phenyliminophenazine, have been separated. The effect of certain substituent groups on the antituberculosis activity in mice of the isomeric pigments is discussed briefly.

IN Part I [1] it was shown that oxidation of 2-aminodiphenylamine hydrochloride with ferric chloride or *p*-benzoquinone gave, among other products, mixtures of 2-anilino-3 : 5-dihydro-3-imino-5-phenylphenazine (anilino*apo*safranine) and its isomer, 2-amino-3 : 5-dihydro-5-phenyl-3-phenyliminophenazine. For the sake of brevity these are named below the 2-isomer and the 3-isomer respectively. In the present paper the oxidative condensation has been applied to a number of derivatives of *o*-phenylenediamine in the hope of discovering substituted phenazines of higher antituberculosis activity and to collect information which would allow biological activity to be related to chemical structure.

In general the crude oxidation products of the amine hydrochlorides contained both the 2- and the 3-isomer. This was not the case when *N*-alkyl- or *N-cyclo*alkyl-*o*-phenylenediamine hydrochlorides were oxidised. Here the only product isolated was the 3-isomer whether ferric chloride or quinone was employed. When the two isomers were formed, *e.g.*, from *N*-alkylphenyl- or *N*-alkoxyphenyl-*o*-phenylenediamines, as a general rule the 3-isomer preponderated in the mixture from the quinone oxidation and the 2-isomer was present in greater quantity in the ferric chloride oxidation product. However, from the oxidation of *N*-*o*-ethoxyphenyl-*o*-phenylenediamine hydrochloride with either reagent only the 2-isomer was isolated. Oxidation of *N*-*p*-ethoxyphenyl-*o*-phenylenediamine hydrochloride with quinone gave the 3-isomer : in the ferric chloride oxidation, a stable iron complex was isolated which gave the colour reactions of a 2-isomer.



2-Isomer



3-Isomer

* Part I, preceding paper.

[1] Barry, Belton, O'Sullivan, and Twomey, preceding paper.

The *o*-nitroaniline intermediates were made by the usual methods, *i.e.*, by refluxing *o*-chloronitrobenzene with the substituted aniline in nitrobenzene.[2] The *N*-alkyl and *N-cyclo*alkyl derivatives of *o*-nitroaniline were formed by heating the mixture of *o*-chloronitrobenzene and the amine in pyridine,[3] a procedure found to be the most satisfactory for the preparation also of the higheralkoxy phenyl-*o*-nitroanilines. Reduction of the nitrocompounds to the *o*-phenylenediamines was effected in a number of ways—by refluxing them with iron filings in aqueous alcohol in the presence of a small quantity of acetic acid or by warming them with Raney nickel and hydrazine [4] or by using Adams catalyst. It was not possible to crystallise *N-p-iso*butoxyphenyl-*o*-nitroaniline or the corresponding *o*-phenylenediamine, and neither of these compounds has been characterised: a dilute hydrochloric acid solution of the amine was nevertheless oxidised by ferric chloride and benzoquinone and the expected 2- and 3-isomers were isolated analytically pure.

Oxidations were carried out by the method described in Part I,[1] but in aqueous alcohol for amine hydrochlorides of low solubility in water. The precipitated pigment hydrochlorides were converted into the bases and chromatographed in benzene on alumina. The *N*-alkyl- and *N-cyclo*alkyl-phenazines were somewhat unstable and appeared to decompose on the alumina column. Colour reactions [with concentrated sulphuric acid and with acetic anhydride (cf. Part I)] of the products, however, which had been purified by recrystallisation indicated that only the 3-isomer was present in each case. In certain instances analytical data were obtained only on the hydrochloride or picrate. The products obtained by ferric chloride oxidation of *N*-methyl-, *N-n*-heptyl- and *N-cyclo*hexyl-*o*-phenylenediamine have already been prepared and incorrectly described as 2-isomers.[5] These are now listed correctly in the Experimental part.

The pigments were all tested for antituberculosis activity in mice infected intravenously with the *Ravenel* bovine strain of *Mycobacterium tuberculosis* (inoculum 0·1 mg.). The drugs were fed in the diet for 14 days, starting on the day of infection. Some idea of the order of activity may be got from the following instance: 2-amino-5-*p*-ethoxyphenyl-3-*p*-ethoxyphenylimino-3:5-dihydrophenazine, fed at a dosage level of 120 mg./kg. for 14 days, produced an increase in median survival time, over the untreated control mice (M.S.T., 14 days), of 90 days. Of the pigments made from *N*-alkyl- and *N-cyclo*alkyl-*o*-phenylenediamines, only the *cyclo*hexyl derivative showed high activity. Pigments derived by oxidation of 2-aminodiphenylamines carrying substituents in the 4′-position all showed enhanced activity and were significantly more active than those derived from the 2-aminodiphenylamines substituted in the 2′-position. On the whole the 3-isomers are more potent antituberculosis agents in mice than the corresponding 2-isomers.

The biological details will be published elsewhere.

Experimental

N-Substituted o-Nitroanilines.—The following is a typical preparation: 4-*n*-Propoxyaniline (20·6 g.), *o*-chloronitrobenzene (21·0 g.), and pyridine (16 c.c.) were heated in a sealed tube at 200° (20 hr.). The mixture was steam-distilled and the residual oil which solidified was recrystallised from methanol (yield, 11 g.; m. p. 43°) (Found: C, 65·7; H, 6·0; N, 10·5. $C_{15}H_{16}O_3N_2$ requires C, 66·2; H, 5·9; N, 10·3%).

The following new derivatives were characterised: *Allyl-*, red oil, b. p. 174—175°/12 mm. (Found: N, 16·0. $C_9H_{10}O_2N_2$ requires N, 15·8%). n-*Propyl-*, red oil, b. p. 170—172°/12 mm. (Found: N, 14·6. $C_9H_{12}O_2N_2$ requires N, 15·55%). cyclo*Pentyl-*, pale yellow oil, b. p. 161—169°/2 mm. (Found: C, 64·1; H, 6·7; N, 13·3. $C_{11}H_{14}O_2N_2$ requires C, 64·1; H, 6·8; N, 13·6%). o-*Ethoxyphenyl-*, dark red oil, b. p. 202—208°/2 mm. (Found: C, 65·8; H, 5·8; N, 10·6. $C_{14}H_{14}O_3N_2$ requires C, 65·1; H, 5·4; N, 10·9%). p-n-*Propoxyphenyl-*, yellow needles (from methanol), m. p. 43° (Found: C, 65·7; H, 6·0; N, 10·5. $C_{15}H_{16}O_3N_2$ requires C, 66·2; H, 5·9; N, 10·3%). p-iso*Propoxyphenyl-*, orange prisms (from light petroleum), m. p. 79—80° (Found: C, 66·0; H, 6·1; N, 10·4%). *p-iso-* and *p-sec.*-Butoxyphenyl-*o*-nitroaniline were obtained as red oils which decomposed on distillation under reduced pressure.

N-Substituted o-Phenylenediamines.—The *o*-nitroanilines were reduced in alcoholic solution

[2] Borrodkin, *J. Appl. Chem.* (*U.S.S.R.*), 1950, **21**, 987.
[3] Burger and Fredericksen, *J. Amer. Chem. Soc.*, 1948, **70**, 416.
[4] Malcolm and Furst, *ibid.*, 1953, **75**, 4334.
[5] Barry, Belton, Chambers, Conalty, Kelly, and Twomey, *Proc. Roy. Irish Acad.*, 1953, **55**, *B*, 157.

by Raney nickel [4] or by Adams catalyst. Where it had been found impossible to purify the nitro-compound completely, the latter was best reduced by iron filings and acetic acid. The following are new: Allyl-, an oil which oxidised very rapidly in the air; it was reduced (Adams catalyst) to the *N*-propyl derivative (see below). *n*-Propyl-, an unstable oil, characterised as the 2 : 4-*dinitrophenyl derivative*, red needles (from ethanol), m. p. 109—110° (Found: C, 57·0; H, 5·2; N, 17·8. $C_{15}H_{16}O_4N_4$ requires C, 57·0; H, 5·1; N, 17·7%). The same compound was got from the hydrogenated *N*-allyl derivative (see above). *cyclo*Pentyl-, b. p. 132—138°/2 mm. [2 : 4-*dinitrophenyl derivative*, orange needles (from ethanol), m. p. 127—128° (Found: C, 59·3; H, 5·5; N, 15·8. $C_{17}H_{18}O_4N_4$ requires C, 59·6; H, 5·3; N, 16·3%)]. o-*Ethoxyphenyl-*, plates (from light petroleum), m. p. 79—80° (Found: C, 72·7; H, 7·2; N, 11·7. $C_{14}H_{16}ON_2,\frac{1}{2}H_2O$ requires C, 72·3; H, 7·1; N, 12·0%). This compound colours immediately in air. p-n-*Propoxyphenyl-*, plates (from light petroleum), m. p. 76° (Found: C, 74·5; H, 7·5; N, 11·5. $C_{15}H_{18}ON_2$ requires C, 74·4; H, 7·4; N, 11·5%). p-iso*Propoxyphenyl-*, needles (from aqueous ethanol), m. p. 74—75° (Found: C, 73·9; H, 7·7; N, 11·5%). p-sec.-*Butoxyphenyl-*, needles (from light petroleum), m. p. 57—59° (Found: C, 74·4; H, 7·8; N, 11·2. $C_{16}H_{20}ON_2$ requires C, 75·0; H, 7·8; N, 11·0%. No stable crystalline *p-iso*-butoxyphenyl derivative could be prepared.

Oxidation of N-*Substituted* o-*Phenylenediamine Hydrochlorides. Isolation of the* 2- *and the* 3-*Isomers.*—The *o*-phenylenediamine hydrochlorides were oxidised (*a*) by ferric chloride and (*b*) by *p*-benzoquinone, and the isomeric phenazine bases were separated on alumina (Merck) columns as described in Part I.[1] On elution with benzene the 3-isomer was always the first obtained; in some cases benzene–ether was required to remove the 2-isomer from the column.

The *phenazines* tabulated have been prepared in sufficient quantity for screening in murine tuberculosis.

5-Aryl-2-arylamino-3 : 5-dihydro-3-iminophenazines (2-isomers) and 2-amino-5-aryl-3-arylimino-3 : 5-dihydrophenazines (3-isomers).

R	Form	Solvent [a]	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
				2-Isomers						
p-C_6H_4Me	Brown	C_6H_6	282—285°	80·3	5·6	13·9	$C_{26}H_{22}N_4$	80·0	5·6	14·4
o-C_6H_4·OMe	Brick-red	C_6H_6	216—219	75·0	5·4	12·8	$C_{26}H_{22}O_2N_4,\frac{1}{4}C_6H_6$	74·7	5·3	12·7
p-C_6H_4·OMe	Orange	C_6H_6	283—285	74·3	5·7	13·0	$C_{26}H_{22}O_2N_4$	73·9	5·2	13·3
o-C_6H_4·OEt	Dark red plates	C_6H_6	140—142	75·3	6·0	11·8	$C_{28}H_{26}O_2N_4,\frac{1}{4}C_6H_6$	75·4	5·8	11·9
p-C_6H_4·OPr^n	,, needles	C_6H_6	230	75·3	6·5	11·4	$C_{30}H_{30}O_2N_4$	75·3	6·3	11·7
p-C_6H_4·OPr^i	,, ,,	EtOH	186—188	75·1	6·8	11·5	,,	,,	,,	,,
p-C_6H_4·OBu^s	Brick-red needles	MeOH	120—123	75·4	6·6	11·0	$C_{32}H_{34}O_2N_4$	75·9	6·7	11·1
p-C_6H_4·OBu^t	Brown-red needles	EtOH	135—137	76·2	6·9	11·0	,,	,,	,,	,,
				3-Isomers						
Me	Red needles	C_6H_6–Lig	176—178	70·3	5·5	23·2	$C_{14}H_{14}N_4$	70·6	5·9	23·5
Allyl [b]	Dark red needles	MeOH	160 [c]	53·3	4·1	18·7	$C_{34}H_{31}O_7N_7,H_2O$	53·6	4·3	18·2
Pr^n [d]	Dark brown	—	—	46·0	5·1	—	[d]	45·4	6·3	—
C_5H_9 [e]	Brown red	Lig	170—171	76·7	7·7	15·7	$C_{32}H_{26}N_4$	76·4	7·5	16·2
n-C_7H_{15}	Dark red needles	—	300	63·4	8·7	—	$C_{26}H_{28}N_4,2HCl$	63·3	8·8	—
p-C_6H_4Me	,, ,,	C_6H_6	243—245	80·5	5·5	14·1	$C_{26}H_{22}N_4$	80·0	5·6	14·4
o-C_6H_4·OMe	Dark red	C_6H_6	227—229	74·8	5·4	12·6	$C_{26}H_{22}O_2N_4,\frac{1}{4}C_6H_6$	74·7	5·3	12·7
p-C_6H_4·OMe [f]	Dark red needles	C_6H_6	228—230	74·7	5·5	12·3	,,	,,	,,	,,
p-C_6H_4·OEt	,, ,,	C_6H_6	225—227	74·7	5·7	12·3	$C_{28}H_{26}O_2N_4$	74·7	5·8	12·4
p-C_6H_4·OPr^n	,, ,,	C_6H_6	194—196	75·2	6·4	11·8	$C_{30}H_{30}O_2N_4$	75·3	6·3	11·7
p-C_6H_4·OPr^i	,, ,,	C_6H_6	215—216	75·0	6·3	11·0	,,	,,	,,	,,
p-C_6H_4·OBu^s	,, ,,	EtOH	183—185	75·6	6·8	11·2	$C_{32}H_{34}O_2N_4$	75·9	6·7	11·1
p-C_6H_4·OBu^t	,, ,,	EtOH	176—178	75·8	6·8	10·9	,,	,,	,,	,,

[a] Lig = ligroin. [b] Picrate. [c] With decomp. [d] Hydrochloride (Found: Cl, 30·5. $C_{16}H_{22}N_4,4HCl,2H_2O$ requires Cl, 29·8%); the unstable base gave unsatisfactory analyses. [e] *cyclo*-Pentyl; the *cyclo*hexyl analogue is described in Part I. [f] Hydrochloride (Found: Cl, 15·5. $C_{26}H_{28}N_4,2HCl$ requires Cl, 15·6%). [g] Gives a *methosulphate*, grass-green needles (from ethanol), m. p. 360° (decomp.) [Found: C, 61·0; H, 5·1; N, 9·8; S, 6·1. $C_{26}H_{22}O_2N_4,(CH_3)_2SO_4$ requires C, 61·3; H, 5·1; N, 10·2; S, 5·8%], and a *monoacetyl derivative*, dark brown needles (from benzene), m. p. 295° (decomp.) (Found: C, 72·5; H, 5·1; N, 12·0. $C_{32}H_{24}O_3N_4$ requires C, 72·4; H, 5·2; N, 12·1%).

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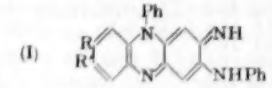
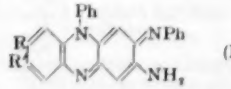
190. *The Oxidation of Derivatives of o-Phenylenediamine. Part III.* Isomeric Phenazine Pigments and apoSafranones obtained by Oxidation of Chlorinated 2-Aminodiphenylamine Hydrochlorides.*

By Vincent C. Barry, J. G. Belton, J. F. O'Sullivan, and Dermot Twomey.

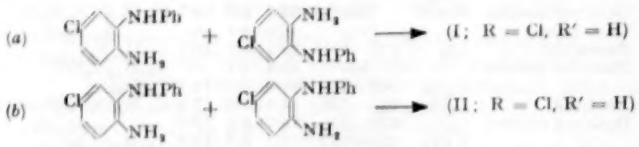
Oxidation of chlorinated 2-aminodiphenylamine hydrochlorides by ferric chloride and by *p*-benzoquinone results in the elimination of chlorine when the latter is present in the 4- or the 5-position, or in both. The products of oxidation are chlorinated anilino*apo*safranines or the corresponding chlorinated isomeric phenazines, or in some cases, a mixture of the two isomers. From a study of the oxidation of five 2-amino-4- or -5-chlorodiphenylamines no generalisation was possible as to the mode of elimination of the chlorine. The *p*-benzoquinone oxidation has been shown to yield also a third type of phenazine, chlorinated *apo*safranones, formed by condensation of the quinone with the diphenylamine derivatives. Some of the dichlorinated phenazines have very high activity in experimental tuberculosis in mice.

In Part I [1] it was shown that oxidation of 2-aminodiphenylamine hydrochloride by ferric chloride or by *p*-benzoquinone gave a mixture of isomers (I and II; R = R′ = H). Oxidation of 2-amino-4- and -5-chlorodiphenylamine hydrochloride had previously been shown [2,3] to give phenazines to which the structures (I; R = H, R′ = Cl) and (I; R = Cl, R′ = H) respectively had been assigned. In both these oxidations a chlorine atom is eliminated but, as the existence of the parent compound (II; R = R′ = H) had not been established at that time, it was not certain that the phenazines obtained by oxidation of the 2-amino-4- and -5-chlorodiphenylamine hydrochlorides were of type (I) rather than of type (II). Further, since chromatography had not been applied in the earlier work,[2,3] it was not improbable that isomeric pigments of types (I) and (II) had been obtained in each case and that the existence of the second isomer had escaped detection.





In the oxidative condensation of 2-amino-5-chlorodiphenylamine hydrochloride the chlorine atom may theoretically be eliminated in two ways, (*a*) or (*b*), as shown :



If it could be shown that the oxidation took course (*a*) or (*b*), then a certain method would be available for the preparation of isomers of types (I) and (II). Accordingly, the oxidation of 2-amino-5-chlorodiphenylamine hydrochloride by ferric chloride and by *p*-benzoquinone was re-investigated. With both reagents the only product identified was the compound (II; R = Cl, R′ = H), which was isolated pure in about 20% yield and gave the colour reactions with sulphuric acid and with acetic anhydride expected [1] for the isomer of type (II).

It will be noted that if the chlorine is eliminated in the same way during oxidation of the 4-chloro-derivative, then the product of the reaction must be in this case the isomer

* Part II, preceding paper.

[1] Barry, Belton, O'Sullivan, and Twomey, *J.*, 1956, 888.
[2] Barry and Belton, *Proc. Roy. Irish Acad.*, 1953, **55**, *B*, 149.
[3] Kehrmann and Guggenheim, *Ber.*, 1901, **34**, 1218.

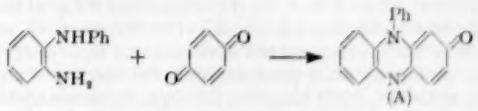
(I; R = H, R′ = Cl). Investigation showed that ferric chloride oxidation of 2-amino-4-chlorodiphenylamine hydrochloride did in fact produce in fair yield only this compound. However, with *p*-benzoquinone there was no evidence of its formation but the isomer (II; R = H, R′ = Cl) was isolated in very poor yield. The latter oxidation was complicated by the fact that the main crystalline compound isolated proved to be a monochloro*apo*safranone (cf. Part I [1]). (These chlorinated *apo*safranones were isolated in almost all cases when chlorinated 2-aminodiphenylamine hydrochlorides were oxidised by *p*-benzoquinone. They are discussed later in this paper.) It was thus clear that the elimination of chlorine during the oxidation could proceed in two ways, and it was therefore expected that oxidation of 2-amino-4 : 5-dichlorodiphenylamine hydrochloride would result in the loss of two chlorine atoms and the production of both isomers (I and II; R = R′ = Cl). However only the latter was formed by oxidation with ferric chloride, and *p*-benzoquinone oxidation yielded only a dichloro*apo*safranone.

Two further compounds containing chlorine in the 4-position were oxidised by both reagents. 2-Amino-4 : 4′-dichlorodiphenylamine hydrochloride gave, with ferric chloride, a mixture of isomers, that of type (II) in greater amount, whereas with *p*-benzoquinone only this isomer was isolated, together with a dichloro*apo*safranone. 2-Amino-4 : 2′ : 4′-trichlorodiphenylamine hydrochloride,[4] gave with ferric chloride the isomer of type (II), while from the *p*-benzoquinone oxidation only a trichloro*apo*safranone could be isolated. On the basis of these results no generalisation seems possible as to the mode of elimination of chlorine during these oxidative condensations.

2-Amino-6-chlorodiphenylamine hydrochloride, which does not lose chlorine on oxidation, gave with ferric chloride only the isomer of type (I), and with *p*-benzoquinone a monochloro*apo*safranone. Finally, 2-amino-4′-chlorodiphenylamine hydrochloride gave a mixture of both types with both reagents, type (I) preponderating when ferric chloride and type (II) when *p*-benzoquinone was used. This result agreed with the behaviour of the parent 2-aminodiphenylamine hydrochloride under similar conditions.

The isomer of type (I) obtained by ferric chloride oxidation of 2-amino-6-chlorodiphenylamine hydrochloride (2-anilino-1 : 6-dichloro-3 : 5-dihydro-3-imino-5-phenylphenazine) gave with concentrated sulphuric acid a red-blue colour in place of the brown-red colour usually obtained with isomers of this class. Any doubt as to its nature was dispelled, however, when in warm acetone in the presence of syrupy phosphoric acid it gave a yellowish-green fluorescent glyoxalinophenazine such as is obtained by condensation of other anilino-*apo*safranines with ketones.[1]

As mentioned in Part I,[1] the filtrate, obtained after removal of the insoluble material resulting from the *p*-benzoquinone oxidation of 2-aminodiphenylamine hydrochloride, contained a number of other products. One such (compound A) was isolated in very small yield as brown plates, m. p. 243—245°, and had the formula, $C_{18}H_{12}ON_2$. In the *p*-benzoquinone oxidations of chlorinated 2-aminodiphenylamine hydrochlorides discussed earlier in this paper, similar materials were sometimes isolated, containing chlorine and,



(A)

perhaps for this reason, less soluble than compound (A). None of these compounds was encountered on ferric chloride oxidation. They were insoluble in alkali and probably did not contain a hydroxyl group. They are probably condensation products of the benzoquinone and the diphenylamine derivative, formed as shown, and compound A was shown to be *apo*safranone [5,6,7] by comparison with a sample. *apo*Safranone was synthesised by Kehrmann and Bürgin's method.[5]

[4] Barry and Belton, *Proc. Roy. Irish Acad.*, 1955, **57**, *B*, 141.
[5] Kehrmann and Bürgin, *Ber.*, 1896, **29**, 1819.
[6] Jaubert, *Ber.*, 1895, **28**, 275.
[7] Kehrmann, *Ber.*, 1897, **30**, 2623.

Chlorinated *apo*safranones were isolated from the *p*-benzoquinone oxidation of 2-amino-4-chloro-, -6-chloro-, -4 : 4'-dichloro-, -4 : 5-dichloro-, -4'-chloro-, and -4 : 2' : 4'-trichlorodiphenylamine hydrochlorides, but not of 2-amino-5-chlorodiphenylamine hydrochloride.

A multiplicity of coloured materials results from the oxidation of 2-aminodiphenylamine bases. On the whole, with the exception of a small amount of the phenazine (II; R = R' = H), these appear to be different from the products of oxidation of the amine hydrochlorides. They have not, however, been thoroughly investigated.

The effect of the chlorine substituents on the activity of the isomers of types (I) and (II) in experimental tuberculosis in mice is interesting. The original anilino*apo*safranine (I; R = R' = H) produces an increased median survival time (M.S.T.) over the controls in mice (M.S.T., 14 days) infected intravenously with the virulent bovine *Ravenel Rv* strain of *Mycobacterium tuberculosis* (inoculum 0·1 mg.) of about 6 days, while the isomer (II; R = R' = H) gives an increased M.S.T. of 12·5 days. The drugs were fed in the diet for the first 14 days at a dosage level of 100 mg./kg. of mouse for (I; R = R' = H) and 125 mg./kg. for (II; R = R' = H). This higher activity of the type (II) isomer is in agreement with the similar findings reported in Part II [8] for other pairs of isomers. When the two isomers prepared from 2-amino-4'-chlorodiphenylamine were screened in mice, an enormous increase in activity was found: the dichlorinated products fed at about the same dosage levels showed a greatly enhanced protective effect, extending the M.S.T. to about 140 days in each case. This enhancement is brought about by the substitution of two chlorine atoms on the periphery of the molecule and may be due in part to an increased fat-solubility which also serves to anchor the molecule in a particular orientation. Where the chlorine is substituted in the phenazine nucleus as in the compounds (I; R = H, R' = Cl) and (II; R = Cl, R' = H), the compounds appear to have negligible activity. The detailed biological experiments will be reported elsewhere.

Experimental

Oxidation of 2-Amino-4'-chlorodiphenylamine Hydrochloride.—(a) *With ferric chloride.* The amine hydrochloride (5 g.) in 1 : 2 aqueous alcohol (150 c.c.) was stirred for 3 hr. with 10% aqueous ferric chloride (200 c.c.). The precipitate was converted into the base with alcoholic sodium hydroxide and chromatographed in benzene on alumina (Merck). Two main red fractions were obtained: the first (0·25 g.), dark red plates (benzene), m. p. 255—257°, was *2-amino-5-chlorophenyl-3-p-chlorophenylimino-3 : 5-dihydrophenazine* (Found: C, 67·1; H, 3·6; N, 13·1; Cl, 16·6. $C_{24}H_{16}N_4Cl_2$ requires C, 66·8; H, 3·7; N, 13·0; Cl, 16·5%). The second (3·5 g.) was the (I) type isomer, *2-p-chloroanilino-5-p-chlorophenyl-3 : 5-dihydro-3-iminophenazine*, a brick red powder (benzene), m. p. 280—283° decomp. (Found: C, 66·6; H, 3·6; N, 13·0; Cl, 16·2%).

(b) *With p-benzoquinone.* The amine hydrochloride (10 g.) in water (350 c.c.) and ethanol (80 c.c.) at 80° was stirred for 3 hr. with an aqueous solution of *p*-benzoquinone (7·0 g. in 250 c.c.). The precipitate (6·7 g.) was converted into the base as above and chromatographed as before. 2 G. of the crude base yielded 1·3 g. of the type (II) isomer and 0·3 g. of the type (I) isomer.

10-p-Chlorophenyl-2 : 10-dihydro-2-oxophenazine.—The filtrate from reaction (b) above was made alkaline with sodium hydroxide, and the dark material separating was chromatographed in benzene on alumina, giving, as main product, dark red needles of the *aposafranone*, m. p. 241—242° (benzene), in about 4% yield based on the diphenylamine hydrochloride (Found: C, 70·1; H, 3·8; N, 9·1; Cl, 11·3. $C_{18}H_{11}ON_2Cl$ requires C, 70·5; H, 3·6; N, 9·1; Cl, 11·6%). The parent *apo*safranone isolated similarly from the *p*-benzoquinone oxidation of 2-aminodiphenylamine hydrochloride has already been described (cf. Part I [1]). It was also prepared by the method of Kehrmann and Bürgin.[5] These authors' description is lacking in some experimental detail which we have supplied:

2 : 10-Dihydro-2-oxo-10-phenylphenazine (apo*safranone*).—*N*-2 : 4-Dinitrophenyl-*N'*-phenyl-*o*-phenylenediamine (5 g.) was mixed with benzoic acid (50 g.) and boiled (15 min.). The cooled mass was ground and extracted repeatedly with dilute aqueous ammonia. The residue was washed with water, dried, extracted with benzene, and chromatographed. The main fraction eluted with benzene weighed 1·1 g. and was analytically pure.

[8] Barry, Belton, O'Sullivan, and Twomey, preceding paper.

Oxidation of 2-*Amino*-5-*chlorodiphenylamine Hydrochloride.*—(a) *With ferric chloride.* This was carried out as above. The only product isolated (20%) was 2-*amino*-7-*chloro*-3 : 5-*dihydro*-5-*phenyl*-3-*phenyliminophenazine* (II; R = Cl, R′ = H), red needles (from benzene), m. p. 264—265° (Found : C, 72·4; H, 4·3; N, 13·8; Cl, 9·0. $C_{24}H_{17}N_4Cl$ requires C, 72·6; H, 3; N, 14·1; Cl, 8·9%).

(b) *With* p-*benzoquinone.* The only product isolated was again (II; R = Cl, R′ = H) in a yield of 20%.

Oxidation of 2-*Amino*-4-*chlorodiphenylamine Hydrochloride.*—(a) *With ferric chloride.* This gave 2-*anilino*-8-*chloro*-3 : 5-*dihydro*-3-*imino*-5-*phenylphenazine* (I; R = H, R′ = Cl) (20% of purified material), dark red needles (from benzene), m. p. 186—187° (Found : C, 72·3; H, 4·3; Cl, 9·2. $C_{24}H_{17}N_4Cl$ requires C, 72·6; H, 4·3; Cl, 8·9%).

(b) *With* p-*benzoquinone.* The oxidation was carried out as usual. Chromatography of the basified material gave one red-purple benzene eluate which on concentration gave reddish-brown crystals, m. p. 303—305° raised to 308—310° on recrystallisation from benzene. The mother-liquor on keeping gave 2-*amino*-8-*chloro*-3 : 5-*dihydro*-5-*phenyl*-3-*phenyliminophenazine* as dark red needles (from benzene), m. p. 243—245°, identified from colour reactions (yield, 2%) (Found : C, 72·5; H, 4·3; N, 14·0; Cl, 8·7%). The other product was the *apo*safranone, 8-*chloro*-3 : 5-*dihydro*-3-*oxo*-5-*phenylphenazine* (Found : C, 70·0; H, 3·9; N, 8·9; Cl, 11·4. $C_{18}H_{11}ON_2Cl$ requires C, 70·5; H, 3·6; N, 9·1; Cl, 11·6%).

Oxidation of 2-*Amino*-6-*chlorodiphenylamine Hydrochloride.*—(a) *With ferric chloride.* The only product identified was 2-*anilino*-1 : 6-*dichloro*-3 : 5-*dihydro*-3-*imino*-5-*phenylphenazine*, reddish-brown crystals (from benzene), m.p. >320° (Found : C, 67·6; H, 4·0; N, 12·6. $C_{24}H_{16}N_4Cl_2,\frac{1}{4}C_6H_6$ requires C, 67·9; H, 3·9; N, 12·4%).

(b) *With* p-*benzoquinone.* The only product obtained from the column was a chloro*apo*safranone, 1-*chloro*-8 : 10-*dihydro*-8-*oxo*-10-*phenylphenazine*, brown-red needles (from benzene), m. p. 267—268° (yield, 60%) (Found : N, 9·4; Cl, 11·6%).

Oxidation of 2-*Amino*-4 : 5-*dichlorodiphenylamine Hydrochloride.*—(a) *With ferric chloride.* The only product identified from the column was 2-*amino*-7 : 8-*dichloro*-3 : 5-*dihydro*-5-*phenyl*-3-*phenyliminophenazine* (II; R = R′ = Cl), red needles (from benzene), m. p. 261—263° (yield, 25%) (Found : C, 67·2; H, 3·8; N, 12·5; Cl, 16·1. $C_{24}H_{16}N_4Cl_2$ requires C, 66·8; H, 3·7; N, 13·0; Cl, 16·5%).

(b) *With* p-*benzoquinone.* The only product obtained crystalline was the dichloro*apo*safranone. It was identified by colour reactions but there was not sufficient for analysis.

Oxidation of 2-*Amino*-4 : 4′-*dichlorodiphenylamine Hydrochloride.*—(a) *With ferric chloride.* Both isomers were obtained after chromatographic separation. 8-*Chloro*-5-p-*chlorophenyl*-2-p-*chlorophenylamino*-3 : 5-*dihydro*-3-*iminophenazine* (15%) was obtained as an orange powder (from benzene), m. p. <330° (Found : C, 62·1; H, 3·3; Cl, 23·1. $C_{24}H_{15}N_4Cl_3$ requires C, 61·9; H, 3·2; Cl, 22·9%). 2-*Amino*-8-*chloro*-5-p-*chlorophenyl*-3-p-*chlorophenylimino*-3 : 5-*dihydrophenazine* was got in 65% yield as dark red needles (from benzene), m. p. 279—282° (Found : C, 62·4; H, 3·6; N, 11·6; Cl, 22·3. $C_{24}H_{15}N_4Cl_3,\frac{1}{4}C_6H_6$ requires C, 63·1; H, 3·4; N, 11·5; Cl, 22·0%).

(b) *With* p-*benzoquinone.* Only the isomer of type (II) and the chlorinated *apo*safranone were identified. The latter, 8-*chloro*-5-p-*chlorophenyl*-3 : 5-*dihydro*-3-*oxophenazine*, was obtained in poor yield as dark red needles (from benzene), m. p. 237—239° (Found : C, 63·1; H, 3·2; N, 8·1; Cl, 21·1. $C_{18}H_{10}ON_2Cl_2$ requires C, 63·3; H, 2·9; N, 8·2; Cl, 20·8%).

Oxidation of 2-*Amino*-4 : 2′ : 4′-*trichlorodiphenylamine Hydrochloride.*—(a) *With ferric chloride.* Only the type (II) isomer, 2-*amino*-8-*chloro*-5-(2 : 4-*dichlorophenyl*)-3-(2 : 4-*dichlorophenylimino*)-3 : 5-*dihydrophenazine*, was isolated; it formed dark red crystals (from benzene), m. p. 236—237° (Found : C, 54·8; H, 2·8; N, 9·5; Cl, 32·1. $C_{24}H_{13}N_4Cl_5,\frac{1}{4}C_6H_6$ requires C, 55·2; H, 2·7; N, 10·0; Cl, 32·0%).

(b) *With* p-*benzoquinone.* Only the chlorinated *apo*safranone, 8-*chloro*-5-(2 : 4-*dichlorophenyl*)-3 : 5-*dihydro*-3-*oxophenazine*, (20%) was identified; it formed dark red needles, m. p. 215—217°, from benzene (Found : C, 57·0; H, 2·8; N, 7·6; Cl, 28·2. $C_{18}H_9ON_2Cl_3$ requires C, 57·5; H, 2·4; N, 7·5; Cl, 28·4%).

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191. *The Decomposition of Inorganic Cyanates in Water.*

By I. A. Kemp and G. Kohnstam.

The simultaneous formation of urea and carbonate from aqueous solutions of ammonium, barium, or sodium cyanate has been studied near 60° and 80°. The ionic strength was virtually constant at 0·25, and $[OH^-]$ ranged from 4×10^{-7} to 2×10^{-3}. The rate of reaction was given by

$$-d[NCO^-]/dt = [NCO^-](k_1'[NH_4^+] + k_3' + k_4'[H_3O^+] + k_5'[HCO_3^-])$$
$$= [HNCO](k_1[NH_3] + k_2[OH^-] + k_4 + k_5[CO_3^{2-}])$$

where the first term accounts for urea formation and the others are responsible for the production of carbonate. A first-order decomposition of urea to cyanate sometimes contributes slightly, and must be taken into account when considering the overall reaction. These rate equations permit an explanation of earlier observations, and other evidence indicates that they can be expected to apply whenever the pH is greater than 2. Borate ions and triethylamine do not affect the rate specifically.

The Brönsted relations for acid and base catalysis apply to k and k', respectively, but general acid or base catalysis is not observed. It therefore seems likely that all the reactions involve nucleophilic addition to cyanic acid in the rate-determining step, with formation of carbonate occurring *via* carbamic acid or the carbamate ion. This mechanism is subject to the restriction that the addition complex resulting from this nucleophilic attack must be capable of forming urea, carbamic acid, or the carbamate ion by proton transfer and bond rupture. Any reactions of these complexes with water or hydroxide ions appear to be too slow to prevent return to the initial reactants. This accounts for the absence of catalysis by borate ions, triethylamine, or cyanate ions in the reactions of cyanic acid.

Inorganic cyanates decompose in aqueous solution to form urea and *carbonate.** When it is borne in mind that reactants and products will be partly present as their conjugate acids or bases, the reactions may be represented by the stoicheiometric equations

$$NCO^- + 2H_2O \rightleftharpoons CO_3^{2-} + NH_4^+ \quad . \quad \text{(i)} \qquad NCO^- + NH_4^+ \longrightarrow CO(NH_2)_2 \quad . \quad \text{(ii)}$$

The kinetics of the formation of urea in aqueous solutions have frequently been studied.[1,2] The reaction is of the first order with respect to ammonium and cyanate ions, but this has only been established over a limited pH range, as all the work was carried out with solutions of ammonium cyanate. According to Wyatt and Kornberg[3] the rate coefficients previously reported for the reaction in water are appreciably in error owing to neglect of the concomitant production of *carbonate*. Many workers have assumed that the reaction involves the combination of ammonium and cyanate ions in the rate-determining step, and the results of kinetic investigations have often been employed to test theories of ionic reactions;[2,4] the good agreement between theory and experiment was accepted as confirmatory evidence of this ionic mechanism. It was, however, pointed out long ago[5] that the observed kinetics are equally consistent with reaction between

* Throughout this paper the term *carbonate* is used collectively, and refers to all forms in which carbonates may be present, *i.e.*, carbonate ions, hydrogen carbonate ions, carbonic acid, and carbon dioxide. Similarly, *cyanate* refers to cyanate ions and cyanic acid, and *ammonium* to ammonium ions and ammonia.

[1] Walker and Hambly, *J.*, 1895, **67**, 746; Walker and Kay, *J.*, 1897, **71**, 489; Janelli, *Gazzetta*, 1953, **83**, 983.

[2] Miller, *Proc. Roy. Soc.*, 1934, **145**, *A*, 288; 1935, **151**, *A*, 188; Warner and Stitt, *J. Amer. Chem. Soc.*, 1933, **55**, 4807; Warner and Warrick, *ibid.*, 1935, **57**, 1491; Svirbely and Warner, *ibid.*, p. 1883; Svirbely and Schramm, *ibid.*, 1938, **60**, 330; Svirbely and Lander, *ibid.*, p. 1613; 1939, **61**, 3538; Svirbely and Rampino, *ibid.*, p. 3534.

[3] Wyatt and Kornberg, *Trans. Faraday Soc.*, 1952, **48**, 454.

[4] Amis, "Kinetics of Chemical Change in Solution," Macmillan, New York, 1949, Chapters 4, 5, 6, and 9.

[5] Chapman and Chattaway, *J.*, 1912, **101**, 170.

ammonia and cyanic acid (these are in equilibrium with ammonium and cyanate ions) and it has since been shown that purely kinetic evidence cannot distinguish between the ionic and non-ionic reactions as both will show the same salt effect, and the same sensitivity to changes in the dielectric constant of the solvent.[6] This problem has been discussed in detail by Frost and Pearson,[7] who drew attention to the analogy between this reaction and the formation of substituted ureas from organic *iso*cyanates, and regarded the non-ionic mechanism as the more probable.

The kinetics of *carbonate* formation have been studied on only a few occasions,[3, 8, 9, 10] and the observations of different workers are not always consistent. It is generally assumed that carbamic acid or the carbamate ion is an intermediate in this reaction, and there is some experimental evidence in favour of this hypothesis.[11] The acid can be expected to be converted into *carbonate* as soon as it is formed, and this also applies to carbamate ions at the high temperatures employed in these experiments.[12]

The present investigation aimed to establish general rate equations for urea and *carbonate* formation in water over a wide range of pH, and to obtain further information about the mechanism of these reactions. The decomposition of ammonium, sodium, and barium cyanates was examined at 60° and, in some cases, at 80°. Sealed containers were employed to avoid any possible loss of carbon dioxide, bases or weak acids being added to some of the reaction mixtures to alter $[OH^-]$ (which ranged from 4×10^{-7} to 2×10^{-3} mole $l.^{-1}$), and also to determine whether they specifically affected the reactions. The decomposition of urea was also studied, though in less detail. $[NCO^-]$ was never greater than 0·055 mole $l.^{-1}$ and the initial ionic strength in all reaction mixtures was adjusted to 0·25 by the addition of potassium nitrate. This value did not change unduly during the course of any one run and concentration units were therefore used when setting up the rate equations. The reactions were followed by analysis for *cyanate* * and *carbonate*; *ammonium* * and urea concentrations were then obtained from the stoicheiometry of the processes and the initial concentrations. Control experiments showed that the urea concentration so calculated was within the experimental error of its value determined by the xanthhydrol method.[13] The concentrations of the various species present at any stage of a kinetic run were calculated from the analytical results, the appropriate thermodynamic equilibrium constants, and the ionic activity coefficients which were taken as 0·705 and 0·686 for univalent ions at 60° and 80°, respectively, and as 0·240 and 0·222 for bivalent ions. Details are given in the Experimental section.

Results

Reaction Products.—The results of this investigation fully confirm Wyatt and Kornberg's observations [3] that *carbonate* formation is not negligible in the decomposition of ammonium cyanate (cf. Run 1, Table 4); the probable reason for the failure of previous workers to observe this has already been discussed by them. In the decomposition of sodium and barium cyanates at 60° the ratio of urea to *carbonate* was substantially the same as found by Masson and Masson.[8] Their observation of a stationary *ammonium* concentration in the decomposition of barium cyanate was based on the assumption that the precipitated barium carbonate represents the total *carbonate* formed. In the present work this assumption leads to a stationary concentration of the same magnitude, but an allowance for the *carbonate* in solution results in *ammonium* concentrations which increase as the reaction proceeds.

* Cf. footnote, p. 900.

[6] Weil and Morris, *J. Amer. Chem. Soc.*, 1949, **71**, 1664.
[7] Frost and Pearson, "Kinetics and Mechanism," Chapman and Hall, London, 1953, pp. 257 *et seq.*
[8] Masson and Masson, *Z. phys. Chem.*, 1910, **70**, 290.
[9] Täufel, Wagner, and Dünwald, *Z. Elektrochem.*, 1928, **34**, 115.
[10] Lister, *Canad. J. Chem.*, 1955, **33**, 426.
[11] Fearon and Dockeray, *Biochem. J.*, 1926, **20**, 13.
[12] Faurholt, *Z. anorg. Chem.*, 1922, **120**, 85.
[13] Fosse, *Compt. rend.*, 1914, **158**, 1076.

Kinetics of Urea Formation.—In all our experiments the rate of urea formation was given by

$$dU/dt = k_1'[NH_4^+][NCO^-] - k_2U \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$= k_1[NH_3][HNCO] - k_2U \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where U is the urea concentration, and $k_1 = k_1'/K_{III}K_{IV}$ with $K_{III} = [HNCO][OH^-]/[NCO^-]$ and $K_{IV} = [NH_3]/[NH_4^+][OH^-]$. The values of the equilibrium constants at ionic strength 0·25 are given on p. 910.

All former workers in this field have reported that the rate of urea formation is given by one or other of these equations, usually (1). The present results show that they apply up to higher pH values than previously examined, and also when no ammonium ions are present initially (cf. Run 18). The second term has often been omitted; its effect on the overall rate is only significant in the later stages of the reaction, or if urea has been added to the reaction mixture.

The rate coefficients, and the appropriate energies and entropies of activation (calculated from the conventional form of the absolute rate equation for reactions in solution [14]) are given in Table 1.

TABLE 1. *Kinetic data for reaction at ionic strength* 0·25.

(Each rate coefficient is the mean from the results of n different reaction mixtures.)

	n		Rate coefficients		E	ΔS^*
	60·10°	80·10°	60·10°	80·10°	(kcal.)	(cal. °K^{-1})
$10^3k_1'$	20	3	1·250 †	9·22 †	23·3	− 4·07
$10^{-2}k_1$	20	3	0·992 †	2·61 †	11·3	−17·8
10^7k_2	6	—	2·62 ‡	—	—	—
$10^6k_3'$	10	2	1·060 ‡	8·67 ‡	24·6	−14·5
$10^{-3}k_3$	10	2	2·204 †	6·88 †	13·3	− 5·69
$10^{-3}k_4'$	10	2	0·67 †	2·33 †	14·6	− 8·82
10^3k_4	10	2	2·70 ‡	9·91 ‡	15·2	−22·5
$10^3k_5'$	10	2	0·292 †	1·187 †	16·1	−28·7
$10^{-3}k_5$	10	2	0·389 †	1·479 †	15·4	− 3·20

† In sec.$^{-1}$ mole^{-1} l. ‡ In sec.$^{-1}$.

k_1' is probably more reliable than k_1, as the latter involves the dissociation constant of cyanic acid which has only been determined at temperatures appreciably lower than those of the present investigation.[9,10,15] Following previous workers,[3] we assumed it to be 2×10^{-4}, irrespective of temperature, and though this may lead to errors in k_1 it does not affect the reliability of the rate equations, as any such errors are cancelled by similar errors in [HNCO]. Other possible errors in the rate coefficients are discussed in the Experimental section (p. 911), but these are probably not very important, as consistent results were obtained under a wide variety of conditions. In any one run the average discrepancy between the observed value of U and that calculated from the mean rate coefficient given in Table 1 was never greater than 3%, and usually less. This is illustrated below for a typical run (a similar comparison for the *carbonate* concentration, C, has also been included; the appropriate rate equations are given on p. 903).

Run 18, initially 0·0496M-NaNCO + 0·0017M-NaOH; temp. 60·10°.

$10^{-2}t$ (sec.)		0	86	193	314	665	1109	1399	1653	1740	2005	2278	2541	2632
10^4U	obs.	—	—	—	—	5	18	24	35	41	52	59	71	75
	calc.	—	—	—	1	6	17	27	38	41	52	63	71	74
10^4C	obs.	3	8	15	21	52	96	129	159	171	204	231	261	271
	calc.	—	8	14	21	48	91	123	153	164	195	225	252	260

Previous work in this field was carried out with solutions of ammonium cyanate. In water, Wyatt and Kornberg [3] found that k_1' was appreciably less than previously reported,[16] and ascribed this observation to the neglect of *carbonate* formation in the earlier studies.

[14] Glasstone, Laidler, and Eyring, "The Theory of Rate Processes," McGraw-Hill, New York, 1941, p. 199.
[15] Naumann, *Z. Elektrochem.*, 1910, **16**, 773.
[16] Warner and Stitt, ref. 2; Warner and Warrick, ref. 2.

This is now confirmed; at 70° and zero ionic strength * our values and theirs agree within the limits of experimental error, and the assumption of negligible *carbonate* in the decomposition of ammonium cyanate leads to a " rate coefficient " which is in good agreement with the earlier, erroneous values (this can be readily verified from the data for Run 1, Table 4). The resulting percentage error in k_1' is virtually the same at 60° and 80°, and the activation energy should therefore not be affected by the neglect of *carbonate* formation; we found E = 24·0 kcal. at zero ionic strength; Svirbely and Warner [2] reported 23·3.

In the decomposition of urea solutions at 60° significant amounts of *carbonate* were formed before the *cyanate* concentration, Cy, became stationary. This is illustrated below.

Run 24, initially 0·1990M-urea; temp. 60·10°.

$10^{-2}t$ (sec.)	0	245	865	1173	1753	2013	2561	2880	3719
10^4Cy	22	29	45	48	50	48	48	47	42
10^5C	30	49	77	101	156	183	233	262	356

As *carbonate* is formed from the *cyanate*, and not directly from urea (cf. p. 904), the urea–*cyanate* equilibrium could not be observed at this temperature. From the rates of the forward and back reactions we find $K' = [NH_4^+][NCO^-]/U = 1·04 \times 10^{-4}$ and $K = [NH_3][HNCO]/U = 2·64 \times 10^{-9}$, at 60·10° and zero ionic strength. Lewis and Randall's data,[17] which are based on Walker and Kay's [1] direct observation of the equilibrium at 100° and the enthalpy change of the reaction,[18] lead to $K' = 1·20 \times 10^{-4}$ under these conditions; presumably equilibrium at 100° is established before any *carbonate* has been formed.

Kinetics of Carbonate *Formation.—Carbonate* was always formed according to the equations

$$dC/dt = k_3'[NCO^-] + k_4'[H_3O^+][NCO^-] + k_5'[HCO_3^-][NCO^-] \quad . \quad . \quad . \quad . \quad (3)$$

$$= k_3[OH^-][HNCO] + k_4[HNCO] + k_5[CO_3^{2-}][HNCO] \quad . \quad . \quad . \quad . \quad (4)$$

where $k_3 = k_3'/K_{III}$, $k_4 = k_4'K_{VIII}/K_{III}$, and $k_5 = k_5'K_V/K_{III}$, with $K_{VIII} = [H_3O^+][OH^-]$, and $K_V = [HCO_3^-][OH^-]/[CO_3^{2-}]$. The values of these equilibrium constants at ionic strength 0·25 are given on p. 910.

TABLE 2. *Instantaneous rates of carbonate formation at* 60·10° *and ionic strength* 0·25.

[Initial reactants: NH_4NCO in Runs 1, 2, 3, and 7; $Ba(NCO)_2$ in 19; NaNCO in all others. Small amounts of the following substances were added to reaction mixtures: NH_3 in Runs 7 and 17; Na_2CO_3 in 2 and 3; $NaHCO_3$ in 12 and 12*a*; NEt_3 in 20; H_3BO_3 in 21.]

Run	1	3	12*a*	2	7	12	21	20	19	14	17	16
$\frac{10^7}{[NCO^-]} \cdot \frac{dC}{dt}$ (sec.$^{-1}$)	240	48	37	36	33	33	33	32	20	11	11	10
$10^4[NCO^-]$	519	530	518	211	507	506	396	355	477	489	496	260
$10^{10}[H_3O^+]$	5000	320	100	120	370	30	40	3	120	10	4	10
$10^4[HCO_3^-]$	2	55	68	73	5	74	67	70	3	2	1	1
$10^4[CO_3^{2-}]$	—	—	—	—	—	6	5	59	—	—	—	—
$10^4[NH_4^+]$	520	469	1	199	514	3	16	7	7	1	5	—
$10^4[NH_3]$	5	64	1	80	70	4	20	106	2	4	61	2
$10^4[NEt_3H^+]$	—	—	—	—	—	—	—	50	—	—	—	—
$10^4[NEt_3]$	—	—	—	—	—	—	—	25	—	—	—	—
$10^4[H_3BO_3]$	—	—	—	—	—	—	104	—	—	—	—	—
$10^4[H_2BO_3^-]$	—	—	—	—	—	—	49	—	—	—	—	—

None of the other species which were present in the various reaction mixtures had any effect on the rate. This is illustrated in Table 2, where instantaneous rates of *carbonate* formation at $[NCO^-] = 1$ are compared for a variety of conditions. These rates were

* Rate coefficient at zero ionic strength $k^\circ = kf_a/f_af_b$, where k is the rate coefficient corresponding to the activity coefficients f. The subscripts a and b refer to the " reactants " (the species whose concentrations appear in the appropriate kinetic term), and x refers to the activated complex which is assumed to carry a charge equal to the sum of the charges of the " reactants."

[17] Lewis and Randall, " Chemical Thermodynamics," McGraw-Hill, New York, 1923, p. 587.
[18] Walker, *Z. phys. Chem.*, 1902, **42**, 207.

obtained from the reaction–time curve, sometimes by extrapolation, and are therefore not very accurate. They do, however, show clearly that the rate is not significantly affected by ammonium ions or ammonia (Runs 12*a* and 2, 14, and 17), triethylammonium ions or triethylamine (Runs 12 and 20), borate ions or boric acid (Runs 12 and 21), or carbonate ions (Runs 12 and 20). It is also apparent that the reaction is of the first order in cyanate ions (Runs 12*a* and 2, 14 and 16), and accelerated by hydroxonium ions (Runs 1, 7, 19, and 14) and hydrogen carbonate ions (Runs 7 and 3, 12*a* and 19).

The rate coefficients, and the appropriate energies and entropies of activation, are given in Table 1. For the reasons already mentioned, each k' is regarded as more reliable than the corresponding k. As before, the other possible errors do not appear to be important; C, when calculated from the mean rate coefficients did not, on the average, differ by more than 3% from the observed value in any one run (illustrated for Run 18). This did not, however, apply in the decomposition of urea solutions. Here C (calc.) was always too high, particularly in the early stages of the reaction. A check of the analytical methods revealed no systematic error, and the observation of a similar, though smaller, discrepancy when carbonate ions were added suggests that the urea may have contained a small amount of some basic impurity or that biuret is formed in the reaction. This substance was present at less than 0·0005M * in our systems, but the neglect of, say, 0·0003M has an appreciable effect on the calculated pH. Further work is necessary before these observations can be explained, but as the predicted value of C was always greater than that observed, there is no evidence for the direct formation of *carbonate* from urea. This is in agreement with the views of other workers.[19]

Our rate equations for *carbonate* formation account for others which have previously been found to apply over more limited ranges of pH. Thus, in strongly alkaline solutions equation (3) reduces to $dC/dt = k_3'[NCO^-]$, a rate law which has already been proposed for such systems.[9,10] The earlier rate coefficients at 100° are in good agreement with our extrapolated value of k_3', and the activation energies are within 1 kcal. At 0°, k_4 agrees closely with the rate coefficient found for the first-order decomposition of cyanic acid;[10] the activation energies differ by less than 1 kcal. At 70°, our value of k_4 is less than that reported by Wyatt and Kornberg,[3] who assumed that only the term involving this parameter is concerned in the production of *carbonate* from unbuffered solutions of ammonium cyanate. We did not find this to be the case, but these authors stressed the approximate nature of their result.

The third term in equation (3) has not been proposed before. It is, however, supported by the results of Masson and Masson,[8] who found *carbonate* formation from sodium cyanate to be autocatalytic (about 65% of the *carbonate* is present as hydrogen carbonate), strongly accelerated by " $NH_4CO_3^-$ " ions and weakly by carbonate ions (small amounts of hydrogen carbonate result from the addition of these ions to water). Their observation of first-order *carbonate* formation from barium cyanate is consistent with our observation that the pH only varies between 7·72 and 7·92 over the course of the reaction at 60° ($[HCO_3^-]$ is very small in this system), and their smaller first-order rate coefficient for the initial *carbonate* formation from sodium cyanate is now seen to arise from the greater pH of this system (cf. Run 14, Table 2).

Lister [10] found that in strongly alkaline cyanate solutions containing added carbonate ions

$$dC/dt = k_3'[NCO^-] + k''[CO_3^{2-}]$$

This is now seen to result from the experimental conditions employed. Initially $[NCO^-] \simeq [OH^-]$, and this near-equality holds throughout the reaction. As $[HCO_3^-] \ll [CO_3^{2-}]$ at high pH values, equation (3) can easily be shown to take the form

$$dC/dt = k_3'[NCO^-] + k_3'K_v[CO_3^{2-}]$$

* The biuret test will not detect smaller quantities

[19] Fawsitt, *Z. phys. Chem.*, 1902, **41**, 61; Burrows and Fawsitt, *J.*, 1914, **105**, 609; Krasil'shchikov, *Zhur. fiz. Khim.*, 1939, **13**, 767; Dirnhuber and Schültz, *Biochem. J.*, 1948, **42**, 628.

under these conditions.* Lister found $10^5k'' = 1{\cdot}1$ sec.$^{-1}$ at 100°; we calculate $10^5k_5'K_w = 1{\cdot}7$ at this temperature and ionic strength 0·25. In view of the large and variable ionic strength of the earlier work, this is regarded as satisfactory.

The combination of our results with those observed in more acid [10] and alkaline solutions [9,10] thus shows that equations (3) and (4) account for the rate of *carbonate* formation from cyanates and cyanic acid, provided the pH is greater than 2.

Discussion

Catalysis by Acids and Bases.—The rate laws for the decomposition of cyanates can be written in the form

$$-dCy/dt = \{NCO^-\}[(k_1')^\circ\{NH_4^+\} + (k_3')^\circ + (k_4')^\circ\{H_3O^+\} + (k_5')^\circ\{HCO_3^-\}] \quad . \quad . \quad (5)$$

$$= \{HNCO\}[k_1^\circ\{NH_3\} + k_3^\circ\{OH^-\} + k_4^\circ + k_5^\circ\{CO_3^{2-}\}] \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where the braces { } refer to activities, and the superscript ° to zero ionic strength.

It seems likely that the first-order terms represent reaction with water, and equation (6) can then be considered to imply reactions of cyanic acid with bases. The rate coefficients increase with increasing base strength and, the activity of water being taken as unity, the "best" Brönsted relation for base catalysis [20] can be written in the form

$$\log_{10}(k^\circ/q) = -1{\cdot}447 + 0{\cdot}3764\log_{10}(p/qK_a) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where k° refers to a base of strength $1/K_a$, K_a is the thermodynamic dissociation constant of its conjugate acid, q the number of centres in the base which can accept a proton with equal ease, and p the number of equivalent, dissociable protons attached to different atoms in the conjugate acid. The rate coefficients calculated from this equation are between three-quarters and twice those observed (see Table 3); this agreement is as good as can be expected from the application of the Brönsted relation to such widely different bases.†

In the reactions of cyanic acid general base catalysis can only apply to *carbonate*

Table 3. *Base strength and rate coefficients for reaction with cyanic acid, at 60·10°.*

Base	p	q	K_a	k° (obs.)	k° (calc.) *
OH^-	1	1	$9{\cdot}62 \times 10^{-14}$	2200	2840
CO_3^{2-}	1	3	$7{\cdot}24 \times 10^{-11}$	389	466
NH_3	1	1	$5{\cdot}07 \times 10^{-9}$	99·2	47·4
H_2O	1	1	1·00	0·0270	0·0357
NEt_3	1	1	$1{\cdot}50 \times 10^{-10}$	—	178
$H_2BO_3^-$	3	1	$9{\cdot}24 \times 10^{-10}$	—	136
NCO^-	1	1	$2{\cdot}00 \times 10^{-4}$	—	0·88
HCO_3^-	2	2	$5{\cdot}19 \times 10^{-4}$ †	—	1·24

* From equation (7). † This is 1000 times the generally accepted value of the first dissociation constant of carbonic acid.[23]

formation (ammonia is not a catalyst in urea formation), and would require a kinetic term, $k_B^\circ\{B\}\{HNCO\}$, to contribute to the rate for each base B present in the reaction mixture. The Brönsted relation derived from k_3°, k_4°, and k_5° does not differ sensibly from equation (7), and leads to the values of k_B° given in Table 3 (for ammonia the rate coefficient for *carbonate* formation should equal k_1°). The expected contribution to C from catalysis by B, *viz.*, $C(B)$, is compared in Table 4 with the difference between the observed value of C and that calculated from equation (4), ΔC, for a number of bases which are present in

* The kinetic term $k_4'[H_3O^+][NCO^-]$ is extremely small.

† This agreement was obtained by taking $\{H_2O\} = 1$, a reasonable procedure in view of the suggestion [21] that the "effective" concentration of water molecules is between 0·13 and 55·5. The more general procedure of taking $\{H_2O\} = [H_2O]$ leads to the prediction of too high a catalytic constant for hydroxide ions, in agreement with other observations.[22]

[20] Brönsted and Pedersen, *Z. phys. Chem.*, 1924, **108**, 185; Brönsted, *Chem. Rev.*, 1928, **5**, 332; Bell, "Acid-Base Catalysis," Clarendon Press, Oxford, 1941, p. 85.

[21] Bell, *Trans. Faraday Soc.*, 1943, **39**, 253; Bell and Higginson, *Proc. Roy. Soc.*, 1949, **197**, *A*, 141.

[22] *Idem*, *op. cit.*, ref. 20, p. 93.

[23] Roughton and Booth, *Biochem. J.*, 1938, **32**, 2049; Olson and Youle, *J. Amer. Chem. Soc.*, 1940, **62**, 1027.

reaction mixtures but do not appear in this equation : $C(HCO_3^-)$ is not quoted, but it is always very small. It can be seen that the catalytic constants employed in the calculation of $C(B)$ are considerably too large when B = NH_3, NEt_3, $H_2BO_3^-$, or NCO^-. Admittedly k_B° calculated from equation (7) may be subject to error but this error should not be as large as a factor of 100, and an error in the same direction for four such widely different bases would be highly fortuitous. It seems much more likely that this relation between base strength and the rate coefficients is a specific one which does not apply to all bases.

TABLE 4. *Base catalysis in carbonate formation at* 60·10°.

(Ionic strength 0·25, concentrations in 10^{-4} mole $l.^{-1}$, t in sec.)

Run 1 : initially 0·0521M-NH_4NCO.

$10^{-2}t$	0	166	242	319	437	630	846	1008	1176	1686	2622	3150
Cy	521	454	427	411	380	340	321	285	265	213	165	147
C (obs.)	3	16	17	21	25	28	31	33	35	44	47	49
ΔC	—	+2	−1	+1	+1	+1	0	−1	0	+3	0	−1
$C(NH_3)$	—	52	71	89	113	146	178	198	216	256	306	326
$C(NCO^-)$	—	23	26	29	32	35	38	39	40	43	45	46

Run 20 : initially 0·0499M-NaNCO + 0·0075M-NEt_3.

$10^{-2}t$	0	97	221	434	551	702	823	1020	1297	1529	1702	2160
Cy	494	487	481	469	461	447	436	417	390	367	344	278
C (obs.)	5	12	18	30	38	50	59	74	98	119	138	185
ΔC	—	+2	+1	0	0	+2	+2	+1	+2	−1	0	−1
$C(NEt_3)$	—	2	4	8	11	15	18	22	29	34	38	49

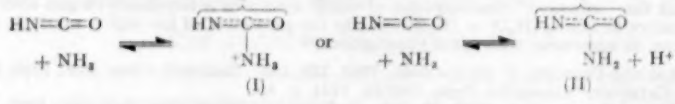
Run 21 : initially 0·0504M-NaNCO + 0·0153M-H_3BO_3.

$10^{-2}t$	0	115	238	415	549	718	984	1283	1506	1625	1837	2147	2366
Cy	485	463	439	396	369	335	282	215	178	161	134	96	80
C (obs.)	18	31	45	73	90	114	151	193	219	231	251	276	289
ΔC	—	−2	−2	+3	−3	+4	+4	+6	−3	+5	+5	+4	+3
$C(H_2BO_3^-)$ ...	—	45	88	140	172	207	250	283	302	309	321	334	340

Alternatively, equation (5) can be considered to imply reactions of cyanate ions with acids. The " best " Brönsted relation for acid catalysis predicts the rate coefficients $(k')^\circ$ with about the same accuracy as equation (7) predicts k°, and it can similarly be shown that the reactions of cyanate ions are not subject to general acid catalysis.

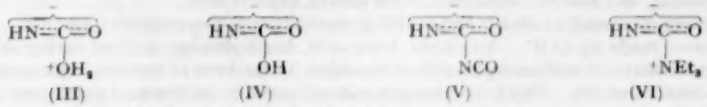
Reaction Mechanism.—The observed kinetics suggest that the four reactions which contribute to the decomposition of *cyanate* involve either a cyanate ion or cyanic acid in the rate-determining step. As each set of rate coefficients follows the Brönsted relation, it seems likely that the reactions occur by the same mechanism irrespective of whether they yield urea or *carbonate*, and the absence of general acid or base catalysis indicates that the reagents do not act by virtue of their ability to donate or accept protons. The connection between nucleophilic activity and base strength [24] allows us to consider another general reaction mechanism, nucleophilic addition to cyanic acid, which permits rate coefficients to follow the Brönsted relation for base catalysis, and it seems probable that this mechanism is operating in the present reactions. This view can only be advanced tentatively at present. It is based on the possibly fortuitous observation that four rate coefficients follow the Brönsted relation, and further work is necessary before it can be finally accepted. On the other hand, our interpretation is consistent with the present findings and also with those of other workers (see next paragraph).

Nucleophilic attack on cyanic acid will occur at the carbon atom, the point of lowest electron density, and the reaction with ammonia can therefore be visualised to occur in the following manner : [25]



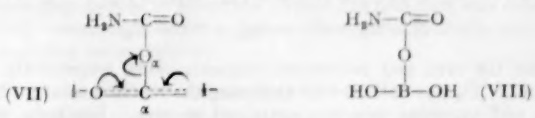
[24] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1953, p. 201.
[25] Lowry, *Trans. Faraday Soc.*, 1934, **30**, 375; Davis and Blanchard, *J. Amer. Chem. Soc.*, 1929, **51**, 1790.

A rapid proton transfer [prototropic change in (I), or proton addition to (II)] then yields urea. Confirmatory evidence for this scheme is supplied by studies of the formation of substituted ureas. As expected, the rates increase with increasing base strength of the amine [7, 26, 27] and with increasing capacity for attracting electrons by substituents in aryl *iso*cyanates.[27] The addition complex resulting from nucleophilic attack by water or hydroxide ions (III or IV) can similarly be expected to undergo rapid proton transfer yielding carbamic acid, and this acid will break down into *carbonate* as soon as it is formed.



(III) (IV) (V) (VI)

It seems likely that this ability of the addition complex to form the product, or a species which is readily converted into it, by simple proton transfer is an essential requirement for reaction. Equation (7) predicts a significant catalysis of *carbonate* formation by cyanate ions and triethylamine (cf. Runs 1 and 20, Table 4), but this was not observed. Steric factors do not oppose the formation of the addition complex (V) or (VI), but this complex can only be converted into carbamic acid or a carbamate ion (which would also readily yield *carbonate* at our reaction temperatures) by a further reaction with water or hydroxide ions (cf. Baker *et al.*[28]). Proton transfer can be expected to occur much more rapidly than reaction with the solvent or its anions, and it seems reasonable to suppose that the intrinsically unstable addition complex has a much greater chance of acquiring a proton



(VII) (VIII)

before it reverts to the initial reactants than of forming a bond with oxygen, either before or after protonation of the imino-group. This view provides an explanation of the catalysis by carbonate ions and the absence of a measurable reaction with borate ions, although such a reaction is predicted by equation (7) (cf. Run 21, Table 4). In the protonated addition complex (VII), the amide group repels electrons less strong than the carboxylate-ion group. Electron shift thus favours the heterolysis of the C_α–O_α linkage, and leads to a carbamate ion and carbon dioxide. In (VIII), however, the corresponding process is much less likely; the hydroxy-groups are less powerful electron donors and the products of the bond-rupture now carry opposite charges. These considerations apply even more strongly to an addition complex of cyanic acid with a metaborate ion.

The proposed reaction mechanism shows many analogies with other carbonyl addition reactions, but it appears that the hydration of cyanic acid (which would lead to carbamic acid by rapid proton transfer) is not subject to general acid–base catalysis, unlike the hydration of acetaldehyde.[29] A reaction similar to *carbonate* formation, the conversion of aryl *iso*cyanates into urethanes, is catalysed by tertiary bases, and it has been proposed that here an addition complex analogous to (VI) reacts with an alcohol molecule.[28] This conclusion is not necessarily incompatible with our view that such a reaction is extremely rare in the present systems. The earlier work was carried out in poorly ionising solvents containing small quantities of alcohol, and the more highly associated solvent and less stable addition complex of the present study are likely to favour the return of the complex to the initial reactants, rather than its solvolysis.

Experimental

Materials and Rate Measurements.—Sodium cyanate (B.D.H., Commercial) was purified by recrystallisation from water at 0°, a large first fraction being discarded; the dried product

[26] Davis and Ebersole, *ibid.*, 1934, **56**, 885.
[27] Naegeli, Tyabji, and Conrad, *Helv. Chim. Acta*, 1938, **21**, 1127.
[28] Baker and Holdsworth, *J.*, 1947, 713; Baker and Gaunt, *J.*, 1949, 9, 19, 27.
[29] Bell and Darwent, *Trans. Faraday Soc.*, 1950, **46**, 34.

contained less than 0·5% of *carbonate*, and no detectable cyanide. Ammonium cyanate was prepared in 0·5M-solution by shaking ammonium chloride (" AnalaR ") with a slight excess of silver cyanate (from urea and silver nitrate) till the supernatant liquid gave only a very faint reaction for chloride; the *carbonate* content of the solution was never greater than 1% of the ammonium cyanate. Barium cyanate was prepared in solution by adding the nitrate to sodium cyanate. Urea (" AnalaR ") was recrystallised twice from ethanol; m. p. 132° (no detectable biuret). Commercial acetone was purified by Conant and Kirner's method.[39] All other materials were commercial products of good purity. " Equilibrium " water was employed in all the solutions, and also as the solvent in the kinetic experiments.

Rates were measured at 60·10° and 80·10° in conventional thermostats (±0·02°). Reaction mixtures were made up at 0°. Ammonia, boric acid, triethylamine, sodium carbonate, sodium hydrogen carbonate, or sodium hydroxide were added (in the form of standard solutions) to some of the reaction mixtures. The ionic strength was adjusted by addition of potassium nitrate to be 0·25 at the reaction temperature, and the cyanate concentration was never greater than 0·055M. 3·75 ml. samples, at 0°, were pipetted into glass tubes which were sealed off so that the free space occupied the same volume as the liquid. The tubes were introduced, with shaking, into the thermostat and removed from time to time, rapidly cooled to −80°, and their contents analysed. The first tubes, which were considered to refer to " zero time," were removed when the solution had attained thermostat temperature (after 2—3 min.), or when enough *carbonate* had been formed to allow of the calculation of $[OH^-]$ with some certainty (cf. p. 909).

Analytical.—The reactions were followed by analysing for $2C + Cy$, and Cy or C, where C and Cy are the *carbonate* and *cyanate* concentrations, respectively. The stoicheiometric equation (i) and (ii) (p. 900) then show that at any stage of the reaction

$$U - U_0 = -(Cy - Cy_0) - (C - C_0)$$
$$N - N_0 = (Cy - Cy_0) + 2(C - C_0)$$

where U and N are the urea and *ammonium* concentrations, respectively, and the subscript refers to " zero time." U_0 was obtained by analysing the reaction mixture before its immersion in the thermostat, and assuming that this contained no urea. Similarly, when no *ammonium* had been added, N_0 was obtained by assuming that all *carbonate*, other than any added, initially, resulted from reaction (i).

(a) *Determination of* 2C + Cy. In the presence of a large excess of acetone, substances which are weak acids in water do not interfere in the titration of hydrochloric acid with alkali. Thus the addition of excess of this acid, followed by back-titration, gave the total basicity of the solution, X (in g.-equiv. l.$^{-1}$). This quantity is independent of any acid–base equilibria which are set up in the reaction mixture, as these merely result in the formation of equivalent amounts of one base from another. Allowing for all the added substances employed, we can therefore write

$$X = 2C + Cy + [NH_3]_i + [NEt_3]_i + [OH^-]_i - [HCO_3^-]_i$$

where the subscript i refers to the concentrations of added species before their participation in acid–base equilibria.

Tubes containing samples of the reaction mixture were cleaned, broken under 200 ml. of neutral acetone, treated with excess of standard hydrochloric acid, then a further 200 ml. of neutral acetone, and titrated with standard sodium hydroxide (lacmoid). Good end-points were obtained if the water content of the titration mixtures was kept low; the acid was therefore made up in 70% (v/v) acetone, and the alkali added from a microburette. The accuracy was 0·4% at $2C + Cy = 0·004$M, and better at higher concentrations.

(b) *Determination of* C. Except in solutions of barium cyanate, C was evaluated by similarly determining the basicity, Y, of a sample from which the cyanate had been removed by precipitation as the silver salt:

$$Y = 2C + [NH_3]_i + [NEt_3]_i + [OH^-]_i - [HCO_3^-]_i$$

5 ml. of approx. 0·1N-silver nitrate, containing ammonium nitrate (40 g. l.$^{-1}$) to prevent the precipitation of silver carbonate, were added to a sample of the reaction mixture, which was made up to 25 ml. After being shaken, some of this mixture was centrifuged and 5 ml. of the supernatant liquid were removed. The basicity of this solution was determined as before, after a few crystals of sodium chloride had been added to precipitate the silver ions present. *Cyanate*

[39] Conant and Kirner, *J. Amer. Chem. Soc.*, 1924, **46**, 245.

was not completely precipitated by this method, and the necessary correction was found by carrying out similar experiments with a solution of approximately the same *cyanate* concentration and with the same solution after it had been diluted five-fold. The quality of the end-point in the final titration could be improved by using less ammonium nitrate, and this was done when the reaction mixtures contained relatively small amounts of *carbonate*. The method could be employed up to $C = 0{\cdot}035$M; its accuracy, which was independent of Cy, was 5% at $C = 0{\cdot}001$M, and better at higher concentrations.

In the decomposition of barium cyanate, virtually all the *carbonate* was precipitated as the barium compound—the correction for the *carbonate* in solution is discussed on p. 910. Here, C was determined by dissolving the washed precipitate from three samples in excess of hydrochloric acid and back-titrating with alkali.

(c) *Determination of* Cy. In the early stages of the decomposition of urea solutions, C was too small for reliable estimation by the methods described above. It was therefore more convenient to evaluate Cy. The method was essentially that proposed by Werner,[31] and the absorption coefficient of the cupric cyanate–pyridine complex in chloroform was examined at 690 mμ, a Unicam S.P. 500 spectrophotometer being used. Nitrate ions interfered slightly, and the " blank cell " was therefore prepared from a solution of the same $[NO_3^-]$ as the solution under test. The accuracy was 5% at $Cy = 0{\cdot}001$M, and better at higher concentrations.

When the reactant was barium cyanate, Cy was determined directly from the supernatant liquid by the method described in (a).

Calculation of Concentrations.—The various species present in a reaction mixture are concerned in the usual acid–base equilibria, and their concentrations can be calculated from the analytical results if $[OH^-]$ and the appropriate equilibrium constants are known. $[OH^-]$ was obtained by the following method. In the first place it is assumed that reactants and products are in the form in which they appear in equations (i) and (ii), and that any other substances are present at their " added " concentrations, *i.e.*, before their participation in any equilibria. The following reactions must then be considered :

$$NCO^- + H_2O \rightleftharpoons HNCO + OH^- \quad \text{(iii)}$$

$$NH_4^+ + OH^- \rightleftharpoons NH_3 + H_2O \quad \text{(iv)}$$

$$CO_3^{2-} + H_2O \rightleftharpoons HCO_3^- + OH^- \quad \text{(v)}$$

$$CO_3^{2-} + 2H_2O \rightleftharpoons H_2CO_3 + 2OH^- \quad \text{(vi)}\ *$$

$$H_2CO_3 \rightleftharpoons CO_2(g) + H_2O \quad \text{(vii)}\ *$$

$$H_2O + H_2O \rightleftharpoons H_3O^+ + OH^- \quad \text{(viii)}$$

$$NEt_3 + H_2O \rightleftharpoons Et_3NH^+ + OH^- \quad \text{(ix)}$$

$$H_3BO_3 + OH^- \rightleftharpoons H_2BO_3^- + H_2O \quad \text{(x)}$$

$$BaCO_3 \rightleftharpoons Ba^{2+} + CO_3^{2-} \quad \text{(xi)}$$

* All dissolved carbon dioxide is assumed to be present as carbonic acid.

Allowing for all the substances which were added to reaction mixtures, we then have

$$[OH^-] = [HCO_3^-] + 2([H_2CO_3] + [CO_2(g)]) - [NH_3] + [HNCO] + [H_3O^+] - [H_3O^+]_i + [OH^-]_i + [Et_3NH^+] - [H_2BO_3^-] - [HCO_3^-]_i + [NH_3]_i \quad (9)$$

where, in the absence of added hydroxide ions, $[OH^-]_i$ and $[H_3O^+]_i$ are the values corresponding to " equilibrium " water.

When no barium ions are present, this equation takes the form

$$N = \frac{1 + K_{iv}[OH^-]}{K_{iv}[OH^-]}\left\{\frac{[OH^-]K_v + 2(1 + K_{vii})K_{vi}}{[OH^-]^3 + [OH^-]K_v + (1 + K_{vii})K_{vi}}C - [OH^-] + \frac{K_{iii}}{K_{iii} + [OH^-]}Cy + \frac{K_{viii}}{[OH^-]} - \frac{K_{viii}}{[OH^-]_i} + [OH^-]_i + \frac{K_{ix}}{K_{ix} + [OH^-]}[NEt_3]_i - \frac{K_x[OH^-]}{1 + K_x[OH^-]}[H_3BO_3]_i - [HCO_3^-]_i + [NH_3]_i\right\}$$

where K_{iii}, K_{iv}, etc., are the equilibrium constants (in concentration units) of processes (iii), (iv), etc., respectively, with terms in $[H_2O]$ included in the constants. Graphical methods were employed to solve this equation for $[OH^-]$, the only unknown parameter. This was less tedious

[31] Werner, *J.*, 1923, **123**, 2577.

than might appear, for several of the terms only enter when the appropriate additions have been made, and some of the others could be neglected without error under the experimental conditions.

In the decomposition of barium cyanate the concentration of *carbonate* in the solution is controlled by the solubility of its barium compound. No acids or bases were added in these experiments, and equation (9) can be written in the form

$$N = \frac{(1 + K_{iv}[OH^-])K_vK_{xi}}{K_{iv}[OH^-]^2[Ba^{++}]}$$

where all negligible terms have been omitted. A correction was, however, necessary before the concentrations of the various species could be calculated. The analytical methods assumed that carbonate precipitation was complete, and the " observed " values of N and C are therefore too small, and those of Cy too large, by an amount $[HCO_3^-]$, as virtually all the *carbonate* in solution is in the form of bicarbonate ions under the existing experimental conditions. The " observed " value of N was employed to obtain a preliminary value of $[OH^-]$ and hence a preliminary value of $[HCO_3^-]$. The resulting " improved " N led to " improved " $[OH^-]$ and $[HCO_3^-]$ values, and the process was repeated till constant values were obtained.

The constants K_{iii}, K_{iv}, etc., were obtained from published thermodynamic equilibrium constants (extrapolated to our reaction temperatures where necessary) and the ionic activity coefficients at ionic strength 0·25. Their values are given below; f_1 and f_2 are the activity coefficients of uni- and bi-valent ions, respectively.

Temp.	f_1	f_2	$10^{10}K_{iii}$	$10^{-4}K_{iv}$	10^4K_v	$10^{10}K_{vi}$	K_{vii}	$10^{13}K_{viii}$	10^5K_{ix}	$10^{-9}K_x$	10^7K_{xi}
60·10°	0·705	0·240	4·81	2·62	6·41	1·19	3·0	1·936	1·29	9·62	1·87
80·10°	0·686	0·222	12·6	2·80	15·7	8·27	3·5	5·357	—	—	—

Rate Coefficients.—k_2 was obtained from studies of the decomposition of urea solutions; the first-order rate law applies over the first 10—12 hr., as the reactions of the cyanate produced do not contribute significantly to the overall rate during this period. Details of a typical run are given below :

t (hr.)	0	1·92	2·63	4·83	7·84	12·2
10^4Cy	0	1·9	2·6	4·4	7·1	11·0
10^7k_2 (sec.$^{-1}$)	—	2·79	2·78	2·56	2·55	2·54

The lack of precision of k_2 does not have a corresponding effect on the reliability of the other rate coefficients. These were obtained from the results observed in the decomposition of cyanates where the term in k_2 is responsible for only a small part of the rate of urea formation.

Once k_2 has been determined, k_1' is the only unknown parameter in equation (1) and can be obtained from its integrated form :

$$k_1' = \frac{U - U_0 + k_2\int_0^t U \,.\, dt}{\int_0^t [NH_4^+][NCO^-] \,.\, dt}$$

The integrals were evaluated graphically.

k_3', k_4', and k_5' were determined by the following method. Integration of equation (2) gives

$$\alpha = (C - C_0 - k_4'\beta)/\gamma = k_3' - k_5'\delta/\gamma$$

where $\beta = \int_0^t [H_3O^+][NCO^-].dt$, $\gamma = \int_0^t [NCO^-].dt$, and $\delta = \int_0^t [HCO_3^-][NCO^-].dt.[H_3O^+]$

is small in Run 13 (cf. Table 3), and provisional values of k_3' and k_5' were obtained from the results as the intercept and slope of the straight-line plot of $(C - C_0)/\gamma$ against δ/γ. These, in conjunction with Run 1, gave a provisional value of k_4'; α in Run 13 could thus be determined, and hence improved values of k_3' and k_5' which, in turn, led to an improved value of k_4'. A repetition of this procedure did not alter the rate coefficients. When sodium cyanate was the reactant, the kinetic term in $[H_3O^+]$ had only a small effect on the rate of carbonate formation, and k_3' and k_5' were determined from the results of such reaction mixtures with the aid of the value of k_4' from Run 1. The mean values of these rate coefficients were then employed in the calculation of k_4' from the observations on systems containing ammonium cyanate as the initial reactant.

The rate coefficients k were obtained from the corresponding values of k' and the equilibrium constants.

The most likely errors in k and k' arise out of the ionic activity coefficients which were employed. These were calculated from the equation proposed by Davies,[32] which is only accurate up to an ionic strength of 0·1.* Any such errors would, however, not be great, and it also seems that they largely cancel each other; our values of k_1 and k_1' agree very closely with those of Wyatt and Kornberg,[3] who used the same equation but did not work at ionic strengths greater than 0·1. It can easily be shown that, although the ionic strength decreases over the course of some of our reactions, this decrease is not large enough to cause significant errors in rate coefficients calculated on the assumption of constant ionic strength.

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UNIVERSITY SCIENCE LABORATORIES, SOUTH ROAD, DURHAM. [*Received, October 10th*, 1955.]

* This equation leads to 0·700 for f_1 at 60°. The use of this figure instead of 0·705 does not alter the values of k', and the change in k is never greater than 1·5%.

[32] Davies, *J.*, 1938, 2093.

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192. *The Synthesis and Reactions of Branched-chain Hydrocarbons. Part X.*† *The Rearrangement of α-Ethynyl Alcohols to Unsaturated Carbonyl Compounds.*

By M. F. ANSELL, J. W. HANCOCK, and W. J. HICKINBOTTOM.

Rearrangement of α-ethynyl alcohols in the presence of formic acid or phosphoric oxide in benzene has been studied. αβ-Unsaturated aldehydes and vinylacetylenes are formed, besides αβ-unsaturated ketones. Some observations on the course of the reaction are made.

THE rearrangement of α-ethynyl alcohols (I) to unsaturated carbonyl compounds is sometimes called the Rupe rearrangement.[1] This reaction has now been applied to eight α-ethynyl alcohols, formic acid or phosphoric oxide suspended in benzene being used

RR'CH·CR''(OH)·C≡CH (I) RR'C:CR''·COMe (II) RR'CH·CR'':CH·CHO (III) RR'C:CR''·C≡CH (IV)

a: R = R' = H, R'' = Me. *d*: R = R' = Me, R'' = Bu^t. *g*: R = R' = Me, R'' = Pr^i.
b: R = R' = H, R'' = Bu^t. *e*: R = R' = H, R'' = CMe$_2$Et. *h*: R = H, R' = Pr^i, R'' = Bu^t.
c: R = H, R' = Me, R'' = Bu^t. *f*: R = H, R' = Me, R'' = CMe$_2$Et.

as reagents. In all the cases studied the unsaturated ketone (II) was formed together with the unsaturated aldehyde (III) and, except in two instances, also the vinylacetylene (IV). Our results are shown in Table 1.

TABLE 1. *Rearrangement of ethynyl alcohols.*

Ethynyl alcohol	Yield of ketone (%)		Yield of aldehyde (%)		Yield of vinylacetylene (%)	
	By H·CO$_2$H	By P_2O_5	By H·CO$_2$H	By P_2O_5	By H·CO$_2$H	By P_2O_5
(I*a*)	*ca.* 2	—	*ca.* 4·5	—	35·0	—
(I*b*) *	33·0	21·0	16·7	7·5	18·3	29·6
(I*c*) *	41·0	27·8	9·6	5·7	17·2	33·2
(I*d*)	Trace	Trace	31·8	15·3	7·5	30·4
(I*e*)	20·3	10·1	8·5	4·3	9·0	34·0
(I*f*)	48·0	12·0	7·0	2·0	6·6	46·0
(I*g*) *.....	6·8	—	2·5	—	0	—
(I*h*)	5·5	—	10·5	—	0	—

* In these rearrangements fission of the ethynyl alcohol to the parent ketone was observed.

† Part IX, *J.*, 1955, 2705.

[1] Johnson, "Chemistry of Acetylenic Compounds," E. Arnold and Co., London, 1949, Vol. I, pp. 127—130.

[3] Hurd and McPhee, *J. Amer. Chem. Soc.*, 1949, **71**, 398.

The rearrangement of 2-methylbut-3-yn-2-ol (I*a*) has been shown by Hurd and McPhee [2] to yield 3-methylbut-3-en-1-yne (IV*a*) and a trace of 3-methylbut-3-en-2-one (II*a*), and Takeshima [3] has isolated a small amount of 3-methylbut-2-enal (III*a*). We confirmed these results and in addition showed the presence of 3 : 7-dimethylocta-2 : 4 : 6-trienal in the product. The last material is formed by self-condensation of 3-methylbut-2-enal.[4]

In the rearrangement of 3 : 4 : 4-trimethylpent-1-yn-3-ol (I*b*) our results are contrary to those of Rupe and Giesler [5] who state that the main product is 3 : 4 : 4-trimethylpent-2-enal (III*b*) together with a small amount of an isomeric aldehyde. We find that the main product is 3-*tert.*-butylbut-3-en-2-one (II*b*), with the unsaturated aldehyde (III*b*) as a minor product. In this reaction fission of the ethynyl alcohol to 3 : 3-dimethylbutan-2-one occurred: such a fission has not previously been recorded under these conditions.

The other six rearrangements (see Table 1) have not been previously reported. The structures of the unsaturated aldehydes were proved by ozonolysis of the aldehydes or the corresponding acids, and the identities of the vinylacetylenes established by hydration to the unsaturated ketones whose structures were proved by ozonolysis. Of these ketones, 3-*tert.*-butylpent-3-en-2-one (II*c*) has been previously reported [6] as the product of the condensation of acetaldehyde with 4 : 4-dimethylpentan-2-one in the presence of alcoholic potassium hydroxide. Our ketone and the corresponding saturated alcohol differ from the compounds thus obtained. It has been shown by Mr. M. A. Davis (in our laboratories), and since the completion of this work,[7] that the condensation of acetaldehyde with 4 : 4-dimethylpentan-2-one occurs at the methyl group of the latter and not at the methylene group as claimed by the earlier workers.

A survey of our results leads us to suggest that although the main product of the Rupe rearrangement is usually the unsaturated ketone [8] (II), this is not invariably so. The formation of an unsaturated aldehyde appears to be favoured by an acumulation of alkyl groups adjacent to the hydroxyl group of the ethynyl alcohol, *e.g.*, in 4 : 4-dimethyl-3-*iso*propylpent-1-yn-3-ol (I*d*). Isolation of the aldehydes is hampered by their tendency to undergo self condensation (cf. the isolation of 3 : 7-dimethyl-2 : 4 : 6-trienal) and by their ease of oxidation which is shown by the isolation of 4 : 4-dimethyl-3-*iso*propylpent-2-enoic acid from the rearrangement of 4 : 4-dimethyl-3-*iso*propylpent-1-yn-3-ol (I*g*).

It was not the original intention of this work to examine the mechanism of the Rupe rearrangement, but our observations are not in accord with some of the hypotheses that have been advanced. It has been suggested [9] that rearrangement in the presence of formic acid depends on the initial dehydration of the ethynyl alcohol (I) to the vinylacetylene (IV) which is then hydrated to the αβ-unsaturated ketone (II). Although this is a possible route we do not consider it to be the exclusive one, because hydration of the vinylacetylenes is slow and incomplete in the presence of formic acid, as is shown in Table 2.

TABLE 2. *Hydration of vinylacetylenes.*

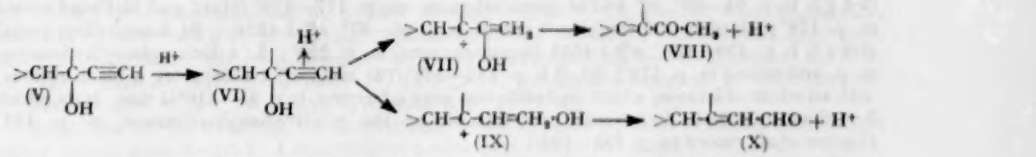
	Formic acid		Mercuric oxide in aq. H_2SO_4	
Vinylacetylene	Unchanged (%)	Unsat. ketone (%)	Unchanged (%)	Unsat. ketone (%)
(IV*b*)	50·5	6·2	—	32·4 *
(IV*c*)	56·4	5·1	32·7	39·7
(IV*d*)	71·1	4·2	21·3	34·9
(IV*e*)	52·8	7·2	26·7	41·0
(IV*f*)	41·1	6·1	16·2	59·0

* 3 : 3-Dimethylbutan-2-one isolated.

The Rupe rearrangement may also be achieved by heating the ethynyl alcohol either with phosphoric oxide in benzene [10, 11] or with a sulphonated resin in aqueous acetic acid.[11]

[3] Takeshima, *J. Sci. Res. Inst. Tokyo*, 1951, **45**, 103.
[4] Fischer *et al.*, *Ber.*, 1935, **68**, 1726; 1937, **70**, 370.
[5] Rupe and Giesler, *Helv. Chim. Acta*, 1928, **11**, 656.
[6] Mosher and Cox, *J. Amer. Chem. Soc.*, 1950, **72**, 3701.
[7] Dubois and Luft, *Compt. rend.*, 1955, **240**, 1540.
[8] Chanley, *J. Amer. Chem. Soc.*, 1948, **70**, 244; Henbest and Woods, *J.*, 1952, 1150.
[9] Price and Meisley, *J. Amer. Chem. Soc.*, 1947, **69**, 1498; Davis and Maloney, *ibid.*, 1949, **71**, 2813.
[10] Saunders, *Org. Synth.*, **29**, 1.
[11] Newman, *J. Amer. Chem. Soc.*, 1953, **75**, 4740.

Under these conditions it does not seem probable that a vinylacetylene would be readily hydrated. We agree with Newman [11] that in these cases the unsaturated ketone arises by an acid-catalysed 1 : 2-shift of the hydroxyl group of the ethynyl alcohol (V ⟶ VIII) and we suggest that the unsaturated aldehyde may arise through a 1 : 3-shift of the hydroxyl group (V ⟶ X), *i.e.*, essentially the mechanism that has been proposed for the Mayer–Schuster rearrangement.[12]



If the Rupe rearrangement occurs as we have suggested, the products of the rearrangement should accompany the normal hydration product obtained by treatment of an ethynyl alcohol with a hot solution of mercuric sulphate in aqueous sulphuric acid. These products have not been previously observed, but, as is shown in Table 3, we have isolated them in

TABLE 3. *Hydration of ethynyl alcohols.*

Ethynyl alcohol	Hydroxy-ketone	Vinylacetylene	Unsat. ketone	Unsat. aldehyde	Unsat. acid
(I*b*) *	71	42	2·4	—	Trace
(I*c*) *	31·7	3·7	46·9	—	Trace
(I*d*)	—	8·8	—	25·3	4
(I*e*)	Trace †	9·2	65	Trace †	—
(I*g*) *	32	—	28	—	Trace
(I*h*)	58	—	9	—	—

* Small amount of parent ketone isolated. † Isolated as 2 : 4-dinitrophenylhydrazone.

six cases. The unsaturated ketone may be partly produced by the hydration of an intermediate vinylacetylene, but it does not seem probable that the unsaturated aldehyde arises in this way as we have not obtained it by hydration of the vinylacetylene under the same conditions.

EXPERIMENTAL

Preparation of Ethynyl Alcohols.—**3 : 4 : 4**-Trimethylpent-1-yn-3-ol gives a **3 : 5-*dinitrobenzoate*,** m. p. **111°**, plates from light petroleum (b. p. **40—60°**) (Found : C, **56·2**; H, **4·7**; N, **8·8**. $C_{15}H_{16}O_6N_2$ requires C, **56·3**; H, **5·0**; N, **8·7%**). **3-*Ethyl*-4 : 4-*dimethylpent*-1-*yn*-3-*ol*** (**73%** yield), b. p. **162—163°**, n_D^{20} **1·4458—1·4460** (Found : C, **77·1**; H, **11·6**. $C_9H_{16}O$ requires C, **77·1**; H, **11·5%**), **3 : 4 : 4-*trimethylhex*-1-*yn*-3-*ol*** (**69%** yield), b. p. **170—171°**, n_D^{20} **1·4535** (Found : C, **77·1**; H, **11·6**. $C_9H_{16}O$ requires C, **77·1**; H, **11·5%**), **3-*ethyl*-4 : 4-*dimethylhex*-1-*yn*-3-*ol*** (**67·3%** yield), b. p. **79—80°/20** mm., n_D^{20} **1·4567—1·4569** (Found : C, **77·7**; H, **11·8**. $C_{10}H_{18}O$ requires C, **77·9**; H, **11·8%**), and **3-*isobutyl*-5-*methylhex*-1-*yn*-3-*ol*** (**38·3%** yield), b. p. **83—84°/18** mm., n_D^{20} **1·4425** (Found : C, **78·5**; H, **11·9**. $C_{11}H_{20}O$ requires C, **78·5**; H, **12·0%**), were prepared by a modification of the method of Froning and Hennion.[13] After evaporation of the ammonia the residue was steam-distilled, the organic layer of the distillate was separated, and the aqueous layer extracted with ether. After drying (Na_2SO_4) of the combined organic material the ether was removed and the residue fractionally distilled.

General Procedure for the Rearrangement of Ethynyl Alcohols.—Method A. A mixture of the ethynyl alcohol (**2·0** moles) and **80%** formic acid (**1600** c.c.) was heated under reflux for **3** hr. After cooling, it was poured into water (**3** l.), the organic layer separated, and the aqueous layer extracted with light petroleum (b. p. **<40°**; **3** × **400** c.c.). The combined organic material was washed with **10%** sodium hydroxide solution (**500** c.c.), then with water (**500** c.c.), and dried (Na_2SO_4). After removal of the solvent the residue was fractionally distilled.

Method B. Phosphoric oxide (**60** g.) was added to a solution of the ethynyl alcohol (**2·0** moles) in dry benzene (**1500** c.c.). The vigorously stirred mixture was heated under reflux for **3** hr., then cooled, and the benzene solution decanted from the brown solid residue. After

[12] Raphael, "Acetylenic Compounds in Organic Synthesis," Butterworths, London, 1955, p. 77.
[13] Froning and Hennion, *J. Amer. Chem. Soc.*, 1940, **62**, 653.

filtering, the solvent was removed and the residue fractionally distilled. The products are recorded in Table 1.

Rearrangement of 2-*Methylbut*-3-*yn*-2-*ol*.—2-Methylbut-3-yn-2-ol (2·0 moles) was rearranged by method A with the following modifications: the reaction mixture, containing a small amount of quinol, was heated under reflux for 1 hr., after which 3-methylbut-3-en-1-yne (46 g.), b. p. 30—35°, n_D^{20} 1·4100 (Hurd and McPhee [8] record b. p. 31—34°, n_D^{20} 1·4105), was distilled off before working up of the residue. Fractional distillation gave: (*a*) 3-methylbut-3-en-2-one (3·5 g.), b. p. 93—96°, n_D^{20} 1·4234 [semicarbazone, m. p. 177—178° (Hurd and McPhee [8] record m. p. 178°; Morgan and Griffiths [14] record b. p. 96—97°, n_D^{20} 1·4224): (*b*) 3-methylbut-3-enal (7·8 g.), b. p. 130—136°, n_D^{20} 1·4538 (semicarbazone, m. p. 220°; 2:4-dinitrophenylhydrazone, m. p. and mixed m. p. 179°) (lit.,[15] b. p. 132—133°/730 mm., n_D^{20} 1·4526); (*d*), a black residue, with an odour of lemons, which on distillation gave a fraction, b. p. 95—110°/1 mm., from which 3:7-dimethylocta-2:4:6-trienal was isolated as the *p*-nitrophenylhydrazone, m. p. 193° (Fischer *et al.*[4] record m. p. 193—194°).

Rearrangement of 3:4:4-*Trimethylpent*-1-*yn*-3-*ol*.—*Method A*. The combined material from three 1·5-molar-scale experiments was fractionally distilled, to yield, with a small forerun and intermediate fractions, (*a*) 2-*tert*.-butylbut-1-en-3-yne (29·8 g.), b. p. 98—98·5°, n_D^{20} 1·4297 (Found: C, 88·7; H, 11·3. Calc. for C_8H_{12}: C, 88·8; H, 11·2%) (lit.,[16] b. p. 98°); (*b*) 3:3-dimethylbutan-2-one (9·1 g.), b. p. 105—107° (2:4-dinitrophenylhydrazone, m. p. and mixed m. p. 126°); (*c*) 3-*tert*.-butylbut-3-en-2-one (186·5 g.), b. p. 142—143·5°, n_D^{20} 1·4340 (semicarbazone, m. p. 169°; 2:4-dinitrophenylhydrazone, m. p. 116—116·5°), for which Hickinbottom, Hyatt, and Sparke [17] record b. p. 142—143°, n_D^{20} 1·4340, semicarbazone, m. p. 165°, and 2:4-dinitrophenylhydrazone, m. p. 116°; (*d*) 3:4:4-trimethylpent-2-enal (95 g.), b. p. 78·5—82°/20 mm., n_D^{20} 1·4675—1·4680 (b. p. 79—80°/20 mm., n_D^{20} 1·4674, on redistillation) [2:4-*dinitrophenylhydrazone*, red needles (from acetic acid), m. p. 238° (Found: C, 54·9; H, 6·0; N, 18·0. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9; N, 18·3%); *p*-*nitrophenylhydrazone*, yellow needles (from aqueous alcohol), m. p. 187° (Found: C, 64·4; H, 7·1; N, 16·0. $C_{14}H_{19}O_2N_3$ requires C, 64·3; H, 7·3; N, 16·1%); semicarbazone, needles (from aqueous alcohol), m. p. 204°] (Wouseng [19] records b. p. 75—78°/15 mm., semicarbazone, m. p. 204—205°; Rupe and Giesler [5] record n^{20} 1·46718, semicarbazone, m. p. 193°).

Reduction of the ketone (*c*) by lithium aluminium hydride gave 3-tert.-*butylbut*-3-*en*-2-*ol*, b. p. 156—157°, n_D^{20} 1·4417 (Found: C, 75·2; H, 12·5. $C_8H_{16}O$ requires C, 75·0; H, 12·6%) {3:5-*dinitrobenzoate*, needles [from light petroleum (b. p. 40—60°)], m. p. 104·5° (Found: C, 56·2; H, 5·4; N, 8·9. $C_{15}H_{18}O_6N_2$ requires C, 55·9; H, 5·6; N, 8·7%)}. Reduction of the ketone (*c*) by sodium in moist ether gave 3:4:4-trimethylpentan-2-ol, b. p. 159—160°, n_D^{20} 1·4355 (lit.,[18] b. p. 70—73°/25 mm., n_D^{20} 1·4343). Its 3:5-*dinitrobenzoate*, plates [from light petroleum (b. p. 40—60°)], had m. p. and mixed m. p. 72—72·5° (Found: C, 55·5; H, 6·4; N, 8·4. $C_{15}H_{20}O_6N_2$ requires C, 55·6; H, 6·2; N, 8·6%): an authentic specimen was prepared from the alcohol obtained by the reduction of 3:4:4-trimethylpentan-2-one with lithium aluminium hydride.

Oxidation of the aldehyde (*d*) by exposure to air or treatment with ammonical silver nitrate solution gave 3:4:4-trimethylpent-2-enoic acid, m. p. 84—85°, which when heated with 80% sulphuric acid for 1 hr. gave the lactone, m. p. 99·5°, of 3-hydroxy-3:4:4-trimethylpentanoic acid; Loquin and Wouseng [20] record the acid, m. p. 85°; Petschnikoff [21] records the lactone, m. p. 99·5°.

Rearrangement of 3-*Ethyl*-4:4-*dimethylpent*-1-*yn*-3-*ol*.—*Method A* (*on a* 2-*molar scale*). Distillation gave the following fractions: (*a*) 48·2 g., b. p. 122—124°, containing some 2:2-dimethylpentan-3-one (isolated as the 2:4-dinitrophenylhydrazone, m. p. and mixed m. p. 174—175°) which on distillation over sodium gave 3-tert.-*butylpent*-3-*en*-1-*yne* (42 g.), b. p. 123—124°, n_D^{20} 1·4470 (Found: C, 88·3; H, 11·6. C_9H_{14} requires C, 88·4; H, 11·6%); (*b*) 3-tert.-*butylpent*-3-*en*-2-*one* (114·8 g.), b. p. 161—161·5°, n_D^{20} 1·4389—1·4390 (Found: C, 77·3; H, 11·4. $C_9H_{16}O$ requires C, 77·1; H, 11·5%) [2:4-*dinitrophenylhydrazone*, m. p. 115·5°, orange-yellow plates (from alcohol) (Found: C, 56·4; H, 6·4; N, 17·3. $C_{15}H_{20}O_4N_4$ requires C, 56·3; H, 6·3; N, 17·5%]; (*c*) 3-*ethyl*-4:4-*dimethylpent*-2-*enal* (27 g.), b. p. 83°/16 mm.,

[14] Morgan and Griffiths, *J.*, 1937, 841.
[15] Fischer, Ertel, and Lowenberg, *Ber.*, 1931, **64**, 30.
[16] Favorskya, *J. Gen. Chem. U.S.S.R.*, 1948, **18**, 52.
[17] Hickinbottom, Hyatt, and Sparke, *J.*, 1954, 2529.
[18] Wheeler, *Univ. Microfilm (Ann. Arbor, Mich.)*, 1941, Publ. No. 380.
[19] Wouseng, *Ann. Chim. (France)*, 1924, **1**, 343.
[20] Loquin and Wouseng, *Compt. rend.*, 1922, **174**, 1711.
[21] Petschnikoff, *J. prakt. Chem.*, 1902, **65**, 178.

n_D^{20} 1·4672 (Found: C, 77·2; H, 11·5. $C_9H_{16}O$ requires C, 77·1; H, 11·5%), colours Schiff's reagent, reduces Fehling's solution [**2** : **4**-*dinitrophenylhydrazone*, m. p. 197·5°, red needles (from acetic acid) (Found: C, 56·2; H, 6·4; N, 17·4. $C_{15}H_{20}O_4N_8$ requires C, 56·2; H, 6·3; N, 17·5%); *semicarbazone*, m. p. 186° (Found: C, 61·1; H, 9·5; N, 21·4. $C_{10}H_{19}ON_3$ requires C, 60·9; H, 9·7; N, 21·3%)].

Reduction of the ketone (*b*) with sodium in moist ether gave **3**-*ethyl*-**4** : **4**-*dimethylpentan*-**2**-*ol*, b. p. 66°/12 mm., n_D^{20} 1·4436 (Found: C, 75·0; H, 13·9. $C_9H_{20}O$ requires C, 74·9; H, 14·0%) [**3** : **5**-*dinitrobenzoate*, m. p. 89·5° (Found: C, 56·7; H, 6·4; N, 8·0. $C_{16}H_{22}O_6N_2$ requires C, 56·8; H, 6·5; N, 8·3%)]. Reduction of the ketone (*b*) with lithium aluminium hydride gave 3-tert.-*butylpent*-**3**-*en*-**2**-*ol*, b. p. 68·5°/14 mm., n_D^{20} 1·4560 (Found: C, 75·8; H, 12·6. $C_9H_{18}O$ requires C, 76·0; H, 12·7%) [**3** : **5**-*dinitrobenzoate*, m. p. 106° (Found: C, 56·9; H, 5·9; N, 8·3. $C_{16}H_{20}O_6N_2$ requires C, 57·1; H, 6·0; N, 8·3%)].

Oxidation of the aldehyde (*c*) by exposure to air or with aqueous-alcoholic ammoniacal silver nitrate gave **3**-*ethyl*-**4** : **4**-*dimethylpent*-**2**-*enoic acid*, m. p. 70° (Found: C, 69·5; H, 10·5. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%), ozonolysis of which gave **2** : 2-dimethylpentan-3-one (**2** : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 174—175°). Reduction of the aldehyde (*c*) with lithium aluminium hydride gave **3**-*ethyl*-**4** : **4**-*dimethylpent*-**2**-*en*-**1**-*ol*, b. p. 88·5°/14 mm., n_D^{20} 1·4590 (Found: C, 76·0; H, 12·8. $C_9H_{18}O$ requires C, 76·0; H, 12·8%) [**3** : **5**-*dinitrobenzoate*, m. p. 75° (Found: C, 57·1; H, 6·1. $C_{16}H_{20}O_6N_2$ requires C, 57·1; H, 6·0; N, 8·3%)].

Rearrangement of **4** : **4**-*Dimethyl*-**3**-iso*propylpent*-**1**-*yn*-**3**-*ol*.—*Method A* (*on a* **1·5**-*molar scale*). Distillation gave the following fractions: (*a*) 3-tert.-*butyl*-**4**-*methylpent*-**3**-*en*-**1**-*yne* (**15·2** g.), b. p. 43°/23 mm., n_D^{20} 1·4428 (b. p. 131°, n_D^{20} 1·4430, after redistillation over sodium) (Found: C, 88·3; H, 12·0. $C_{10}H_{16}$ requires C, 88·2; H, 11·8%); (*b*) 3-tert.-*butyl*-**4**-*methylpent*-**3**-*en*-**2**-*one* (**6·1** g.), b. p. 75—75·5°/23 mm., n_D^{20} 1·4487 (Found: C, 78·0; H, 12·0. $C_{10}H_{18}O$ requires C, 77·9; H, 11·8%) [**2** : **4**-*dinitrophenylhydrazone*, m. p. 101·5—102°, yellow-orange plates from aqueous alcohol (Found: C, 57·3; H, 6·5; N, 16·4. $C_{16}H_{22}O_4N_4$ requires C, 57·5; H, 6·6; N, 16·7%]; (*c*) **4** : **4**-*dimethyl*-**3**-iso*propylpent*-**2**-*enal* (**73·4** g.), b. p. 98—98·5°/19 mm., n_D^{20} 1·4687—1·4690 (Found: C, 77·7; H, 11·8. $C_{10}H_{16}O$ requires C, 77·9; H, 11·8%) [**2** : **4**-*dinitrophenylhydrazone*, m. p. 200·5°, red needles from benzene (Found: C, 57·3; H, 6·7; N, 16·6. $C_{16}H_{22}O_4N_4$ requires C, 57·5; H, 6·6; N, 16·7%); *semicarbazone*, m. p. 208° (Found: C, 62·6; H, 9·9; N, 19·8. $C_{11}H_{21}ON_3$ requires C, 62·5; H, 10·0; N, 19·9%)].

Reduction of the aldehyde by lithium aluminium hydride gave **4** : **4**-*dimethyl*-**3**-iso*propylpent*-**2**-*en*-**1**-*ol*, b. p. 101°/13 mm., n_D^{20} 1·4626 (Found: C, 76·6; H, 12·8. $C_{10}H_{20}O$ requires C, 76·8; H, 12·9%) [**3** : **5**-*dinitrobenzoate*, m. p. 92° (Found: C, 58·2; H, 6·4; N, 8·2. $C_{17}H_{22}O_6N_2$ requires C, 58·3; H, 6·3; N, 8·0%)]. Oxidation of the aldehyde as for **3** : **4** : 4-trimethylpent-2-enal gave **4** : **4**-*dimethyl*-**3**-iso*propylpent*-**2**-*enoic acid*, m. p. 128° (Found: C, 70·6; H, 10·6%; *M*, 170. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·7%; *M*, 170), ozonolysis of which gave **2** : **4** : 4-trimethylpentan-3-one (**2** : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 165—166°). This acid (**5·4** g.) was also obtained by extraction of the residual tar from the distillation with 10% sodium hydroxide solution.

Rearrangement of **3** : **4** : **4**-*Trimethylhex*-**1**-*yn*-**3**-*ol*.—*Method A* (*on a* **2**-*molar scale*). Distillation gave the following fractions: (*a*) **3**-(**1** : **1**-*dimethylpropyl*)*but*-**3**-*en*-**1**-*yne* (**23·8** g.), b. p. 127—128°, n_D^{20} 1·4413 (b. p. 128°, n_D^{20} 1·4410, on redistillation over sodium) (Found: C, 88·3; H, 11·8. C_9H_{14} requires C, 88·4; H, 11·6%); (*b*) a fraction, b. p. 163—166°, which when shaken with excess of aqueous ammoniacal silver nitrate and redistilled gave **3**-(**1** : **1**-*dimethylpropyl*)*but*-**3**-*en*-**2**-*one* (**57** g.), b. p. 163—163·5°, n_D^{20} 1·4395 (Found: C, 77·2; H, 11·4. $C_9H_{16}O$ requires C, 77·1; H, 11·5%) [**2** : **4**-*dinitrophenylhydrazone*, m. p. 135°, yellow needles from aqueous alcohol (Found: C, 56·2; H, 6·4; N, 17·7. $C_{15}H_{20}O_4N_4$ requires C, 56·2; H, 6·3; N, 17·5%)]; (*c*) **3** : **4** : **4**-*trimethylhex*-**2**-*enal* (**26·1** g.), b. p. 87—89°/18 mm., n_D^{20} 1·4722 (b. p. 90—91°/20 mm., n_D^{20} 1·4728, for an analytical sample) (Found: C, 76·8; H, 11·6. $C_9H_{16}O$ requires C, 77·1; H, 11·5%), colours Schiff's reagent and reduces Fehling's solution [*semicarbazone*, plates (from aqueous alcohol), m. p. 172° (Found: C, 61·2; H, 9·6; N, 21·0. $C_{10}H_{19}ON_3$ requires C, 60·9; H, 9·7; N, 21·3%); **2** : **4**-*dinitrophenylhydrazone*, red needles (from acetic acid), m. p. 196·5° (Found: C, 56·1; H, 6·2; N, 17·5. $C_{15}H_{20}O_4N_4$ requires C, 56·3; H, 6·3; N, 17·5%)].

Oxidation of the aldehyde as for **3** : **4** : 4-trimethylpent-2-enal gave **3** : **4** : **4**-*trimethylhex*-**2**-*enoic acid*, m. p. 71—72° (Found: C, 69·3; H, 10·3. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%), ozonolysis of which gave **3** : 3-dimethylpentan-2-one (**2** : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 112°).

Rearrangement of **3**-*Ethyl*-**4** : **4**-*dimethylhex*-**1**-*yn*-**3**-*ol*.—*Method A* (*on a* **1·5**-*molar scale*). Distillation gave fractions: (*a*) **3**-(**1** : **1**-*dimethylpropyl*)*pent*-**3**-*en*-**1**-*yne* (**14·9** g.), b. p. 41—42°/12

mm., n_D^{20} 1·4507 (b. p. 148°, n_D^{20} 1·4500, after distillation over sodium) (Found : C, 88·2; H, 11·9. $C_{10}H_{16}$ requires C, 88·2; H, 11·8%); (*b*) **3-(1 : 1-*dimethylpropyl*)*pent*-3-*en*-2-*one*** (110·9 g.), b. p. 64—65°/12 mm., n_D^{20} 1·4457 (Found : C, 78·0; H, 11·8. $C_{10}H_{18}O$ requires C, 77·9; H, 11·8%); (*c*) **3-*ethyl*-4 : 4-*dimethylhex*-2-*enal*** (16·2 g.), b. p. 92—93°/12 mm., n_D^{20} 1·4724 (Found : C, 78·4; H, 11·8. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%), colours Schiff's reagent, reduces Fehling's solution [***semicarbazone***, needles (from aqueous alcohol), m. p. 169° (Found : C, 62·6; H, 9·9; N, 20·0. $C_{11}H_{21}ON_3$ requires C, 62·5; H, 10·0; N, 19·9%); 2 : 4-***dinitrophenylhydrazone***, bright red (from acetic acid), m. p. 156° (Found : C, 57·4; H, 6·5; N, 16·8. $C_{18}H_{22}O_4N_4$ requires C, 57·5; H, 6·6; N, 16·7%)], giving on ozonolysis 4 : 4-dimethylhexan-3-one (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 86°).

Reduction of the ketone with lithium aluminium hydride gave **3-(1 : 1-*dimethylpropyl*)*pent*-3-*en*-2-*ol***, b. p. 91°/22 mm. (Found : C, 77·1; H, 13·0. $C_{10}H_{20}O$ requires C, 76·9; H, 12·9%) [3 : 5-***dinitrobenzoate***, m. p. 88·5°, plates from light petroleum (Found : C, 58·1; H, 6·2; N, 8·2. $C_{17}H_{22}O_6N_2$ requires C, 58·3; H, 6·3; N, 8·0%)].

Rearrangement **4-*Methyl*-3-iso*propylpent*-1-*yn*-3-*ol***.—*Method A* (*on a 2·0-molar scale*). Distillation gave the following fractions : (*a*) di*iso*propyl ketone (6·0 g.), b. p. 121—124°, n_D^{20} 1·4010 (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 95—96°); (*b*) **4-methyl-3-*iso*propylpent**-3-en-2-one (190·5 g.), b. p. 169—169·5°, n_D^{20} 1·4448—1·4450 (Hickinbottom, Hyatt, and Sparke [17] record b. p. 67·5°/15 mm., n_D^{20} 1·4450; (*c*) **4-*methyl*-3-iso*propylpent*-2-*enal*** (7·2 g.), b. p. 85—86°/12 mm., n_D^{20} 1·4728 (Found : C, 76·9; H, 11·4. $C_9H_{14}O$ requires C, 77·1; H, 11·5%), colours Schiff's reagent, reduces Fehling's solution [***semicarbazone***, plates (from aqueous alcohol), m. p. 166° (Found : C, 61·1; H, 9·6; N, 21·1. $C_{10}H_{19}ON_3$ requires C, 60·9; H, 9·7; N, 21·3%); 2 : 4-***dinitrophenylhydrazone***, m. p. 180° (Found : C, 56·1; H, 6·2; N, 17·4. $C_{15}H_{20}O_4N_4$ requires C, 60·9; H, 9·7; N, 21·3%)], giving on ozonolysis di*iso*propyl ketone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 95—96°).

Rearrangement of **3-iso*Butyl*-5-*methylhex*-1-*yn*-3-*ol***.—*Method A* (*on a 1·5-molar scale*). Distillation gave the following fractions : (*a*) **3-iso*butyl*-5-*methylhex*-3-*en*-2-*one*** (138·8 g.), b. p. 84—84·5°/14 mm., n_D^{20} 1·4500 (Found : C, 78·7; H, 11·9. $C_{11}H_{20}O$ requires C, 78·5; H, 12·0%) [2 : 4-***dinitrophenylhydrazone***, m. p. 130°, orange plates from aqueous alcohol (Found : C, 58·5; H, 6·9; N, 16·2. $C_{17}H_{24}O_4N_4$ requires C, 58·6; H, 6·9; N, 16·1%)]; (*b*) 3-iso*butyl*-5-*methylhex*-2-*enal* (27·7 g.), b. p. 102—103°/14 mm., n_D^{20} 1·4650 (Found : C, 78·3; H, 11·9. $C_{11}H_{20}O$ requires C, 78·5; H, 12·0%) colours Schiff's reagent, reduces Fehling's solution [***semicarbazone*** (from aqueous alcohol), m. p. 115—116° (Found : C, 64·3; H, 10·2; N, 18·8. $C_{12}H_{23}ON_3$ requires C, 64·0; H, 10·3; N, 18·6%); 2 : 4-***dinitrophenylhydrazone***, red needles (from alcohol), m. p. 137° (Found : C, 58·4; H, 6·8; N, 16·4. $C_{17}H_{24}O_4N_4$ requires C, 58·6; H, 6·9; N, 16·1%)]. Reduction of the ketone with lithium aluminium hydride gave 3-iso***butyl*-5-*methylhex*-3-*en*-2-*ol***, b. p. 91°/16 mm., n_D^{20} 1·4480 (Found : C, 77·7; H, 12·9. $C_{11}H_{22}O$ requires C, 77·6; H, 13·0%) [3 : 5-dinitrobenzoate, m. p. 53°, needles from light petroleum (b. p. <40°)]; ozonolysis of the aldehyde gave di*iso*butyl ketone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 92°).

Hydration of Vinylacetylenes.—Method A. The vinylacetylene (0·2 mole) was treated as in the rearrangement of ethynyl alcohols by method A.

Method B. The vinylacetylene (0·25 mole) was added to a stirred solution of mercuric oxide (1·8 g.) in concentrated sulphuric acid (12 c.c.) and water (120 c.c.) at 80°. After being heated and stirred for 3 hr. the mixture was steam-distilled. The organic layer of the distillate was separated and the aqueous layer extracted with ether (3 × 20 c.c.). The ether was removed from the dried ($MgSO_4$) combined organic material, and the residue fractionally distilled. The products obtained are in Table 2, and their physical constants are recorded above.

Ozonolysis of the Unsaturated Ketones.—Ozonised air was bubbled through a solution of the unsaturated ketone (5 g.) in dry chloroform (25 c.c.) for 24 hr. The solvent was then removed at 30° and a mixture of zinc dust (2·0 g.) and water (50 c.c.) added. After 1 hr. at room temperature the mixture was heated under reflux while air was aspirated through it into a warm aqueous-alcoholic sulphuric acid solution of 2 : 4-dinitrophenylhydrazine (except in cases marked * when a solution of dimedone was used). The identity of the carbonyl derivative formed (*A*) is shown below. The mixture was then extracted with ether, and, after drying (Na_2SO_4), the ethereal extract was added to lithium aluminium hydride (1 g.) in ether (20 c.c.). After 1 hr. the mixture was worked up in the usual way and the reduction product (*ca.* 1·5 g.) was shaken for 4 hr. with a solution of periodic acid (1·5 g.) in alcohol (5 c.c.) and water (12 c.c.). Air was then aspirated through the solution into 2 : 4-dinitrophenylhydrazine reagent, and the precipitate formed filtered off and chromatographed in light petroleum (b. p. 40—60°)–benzene on alumina.

Elution with the same solvent gave the 2 : 4-dinitrophenylhydrazone B together with acetaldehyde 2 : 4-dinitrophenylhydrazone.

Unsaturated ketone	A	B
CH_2:CBu^t·COMe*	CH_2O	Bu^t·CHO
CHMe:CBu^t·COMe	Me·CHO	Bu^t·CHO
CMe_2:CBu^t·COMe	$COMe_2$	Bu^t·CHO
CMe_2Et·C(:CH_2)·COMe*	CH_2O	CMe_2Et·CHO
CMe_2Et·C(:CHMe)·COMe	Me·CHO	CMe_2Et·CHO
CMe_2:CPr^i·COMe	$COMe_2$	Pr^i·CHO
CHPr^i:CBu^t·COMe	Pr^i·CHO	Bu^t·CHO

Hydration of Ethynyl Alcohols.—The ethynyl alcohol (1·0 mole) was added dropwise during 2 hr. to a stirred boiling solution of mercuric oxide (15 g.) in concentrated sulphuric acid (100 c.c.) and water (500 c.c.). Heating and stirring were continued for a further 3 hr. and the mixture then steam-distilled. The organic layer was separated and the aqueous layer extracted with ether. The combined organic material was dried (Na_2SO_4), the ether removed, and the residue fractionally distilled. Acidic material was extracted from the residue from the distillation. The products and yields are in Table 3. The physical constants of the products are described above or elsewhere, with the exception of *3-hydroxy-4-methyl-3-isopropylpentan-2-one*, b. p. 82°/18 mm., n_D^{20} 1·4412 (Found: C, 68·2; H, 11·3. $C_9H_{18}O_2$ requires C, 68·3; H, 11·5%) (no carbonyl derivative could be obtained), and *3-isobutyl-3-hydroxy-5-methylhexan-2-one*, b. p. 94·5°/14 mm. (Found: C, 71·0; H, 11·9; active H, 0·52. $C_{11}H_{22}O_2$ requires C, 70·9; H, 11·9; active H, 0·54%) [*semicarbazone*, m. p. 152—153°, plates from aqueous alcohol (Found: C, 59·1; H, 10·2; N, 17·0. $C_{12}H_{25}O_2N_3$ requires C, 59·2; H, 10·4; N, 17·3%); *2 : 4-dinitrophenylhydrazone*, m. p. 162°, yellow needles from alcohol (Found: C, 55·5; H, 7·2; N, 15·3. $C_{17}H_{26}O_6N_4$ requires C, 55·7; H, 7·2; N, 15·3%)].

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193. *The Synthesis of Pyrimidin-5-yl Sulphides and Disulphides. Part II.**

By G. R. BARKER and NYDIA G. LUTHY.

The synthesis of di-(6-amino-2 : 4-dihydroxypyrimidin-5-yl) disulphide is reported. This compound is also produced during the formation of 6-amino-2 : 4-dihydroxypyrimidin-5-yl purin-6-yl sulphide from 6-mercaptopurine and 6-amino-5-bromouracil. Analogous reactions are described for derivatives of 1-methyluracil. An explanation is sought for the anomalous behaviour of certain pyrimidines.

IN Part I,* convenient syntheses of di-(2 : 4 : 6-trihydroxypyrimidin-5-yl) disulphide and di-(6-amino-2 : 4-dihydroxypyrimidin-5-yl) sulphide were described. We have since discovered early descriptions[2,3] of " thiodialuric acid " which are of interest in connection with our work. Repetition of the preparations described by the German workers yielded a material which did not correspond to " thiodialuric acid," but was identical spectroscopically and polarographically with our di-(2 : 4 : 6-trihydroxypyrimidin-5-yl) disulphide.

In our previous experiments it was found that although thiourea reacts satisfactorily with 6-amino-5-bromouracil, decomposition of the resulting *iso*thiourea yields a monosulphide instead of a disulphide. Since, for the purpose of biological tests, it is desirable to have the two pyrimidine rings joined by a reversibly dissociable linkage, further

* *J.*, 1954, 4206, is to be regarded as Part I.

[1] Barker, Luthy, and Dhar, *J.*, 1954, 4206.
[2] Nencki, *Ber.*, 1871, **4**, 722.
[3] Trzcinski, *Ber.*, 1883, **16**, 1057.

experiments have been carried out and a satisfactory synthesis of di-(6-amino-2 : 4-dihydroxypyrimidin-5-yl) disulphide, which has already been described briefly,[4] is now reported fully.

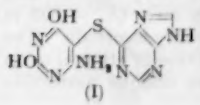
Introduction of the mercapto-group at the 5-position of uracil has recently been effected by displacement of the diazonium residue.[5] We found [1] that the halogen atom in 5-bromouracil is not displaced by thiourea, which is considered a strong nucleophilic reagent [6] and it therefore seemed possible that replacement of a diazonium residue might be effective in bringing about substitution at the 5-position of 6-aminouracil. However, after treatment of 5 : 6-diaminouracil with cold nitrous acid, there was no reaction with sodium disulphide. This may be due to a side reaction leading to the formation of pyrimidinotriazole derivatives.[7] Further experiments indicated that the inability of a reagent to effect substitution is not due simply to lack of susceptibility to nucleophilic attack. Thus, although displacement of halogen by the thiocyanate ion yields satisfactorily a disulphide derived from 5-mercaptobarbituric acid,[3] interaction of 4-amino-5-bromouracil with ammonium thiocyanate was very sluggish, and only small amounts of disulphide were detected polarographically in the resulting solution. Similarly, little or no reaction occurred between the bromo-compound and potassium ethyl xanthate; [8] with potassium hydrogen sulphide, the bromine atom was removed and 6-aminouracil was isolated as the main product. However, 6-amino-5-bromouracil reacts readily with sodium disulphide in 95% ethanol. A dark green colour, initially produced, quickly faded and then crystalline di-(6-amino-2 : 4-dihydroxypyrimidin-5-yl) disulphide gradually separated. After reprecipitation by acidification of an alkaline solution, the material was characterised as a disulphide by reduction at the dropping-mercury electrode.

There is little doubt that the reaction between sodium disulphide and 6-amino-5-bromouracil is a nucleophilic attack by the disulphide ion. However, a nucleophilic mechanism is difficult to reconcile with the failure to effect substitution by the reagents already mentioned. This may be due to the fact that 6-amino-5-bromouracil behaves in certain circumstances as a " positive-halogen " compound, as it liberates iodine immediately from potassium iodide solution. On the other hand, 5-bromouracil liberates iodine only very slowly. This has the effect of partly neutralising the normal polarisation of the $C_{(5)}$–Br bond, as suggested in analogous cases by Robertson and Waters.[9] This behaviour as a " positive-halogen " compound may explain the replacement of bromine by hydrogen on treatment of 6-amino-5-bromouracil with potassium hydrogen sulphide. Similar considerations may also explain the fission of a $C_{(5)}$–S bond in the conversion of 5-amidinothio-6-amino-2 : 4-dihydroxypyrimidine into a monosulphide.[1] It thus appears that potentially tautomeric groups at the 4- and the 6-position, which were shown in Part I to be necessary to facilitate reaction at the 5-position with thiourea (normally considered to be a nucleophilic substitution), may affect the reactivity at that carbon atom in a complex manner.

To investigate further the usefulness of sodium disulphide in substitution, experiments were carried out with a number of 5-bromopyrimidines. 6-Amino-5-bromo-1-methyluracil, but not 5 : 5-dibromohexahydro-6-imino-1-methyl-2 : 4-dioxopyrimidine, reacted satisfactorily to yield the corresponding disulphide. This difference between the mono- and di-bromo-compounds was unexpected since both the above compounds react with thiourea to give the same *iso*thiourea. (Hydrolysis of the *iso*thiourea from 6-amino-1-methyluracil gave an intractable oil from which no sulphide or disulphide could be obtained.) As was to be expected 5-bromouracil also failed to react with sodium disulphide; in this case the typical green of the intermediate was produced as with 6-amino-5-bromouracil, but on the disappearance of the colour, the starting material was regenerated. No evidence is available to indicate the nature of these coloured complexes.

[4] Barker and Luthy, *Chem. and Ind.*, 1955, 983.
[5] Bardos, Herr, and Enkoji, *J. Amer. Chem. Soc.*, 1955, **77**, 960.
[6] Pearson, Langer, Williams, and McGuire, *J. Amer. Chem. Soc.*, 1952, **74**, 5130.
[7] Roblin, Lampen, English, Cole, and Vaughan, *ibid.*, 1945, **67**, 290.
[8] Cf. Djerassi, Gorman, Maskley, and Oldenburg, *ibid.*, 1955, **77**, 568.
[9] Robertson and Waters, *J.*, 1947, 492.

To explore further the potentialities as chemotherapeutic agents of sulphides and disulphides of the pyrimidine series, attention was turned to the synthesis of unsymmetrical compounds. In view of the use of 6-mercaptopurine in treating leukæmia, attempts have been made to prepare 6-purinyl 5-pyrimidinyl sulphides. However, interaction of 6-mercaptopurine and 6-amino-5-bromouracil in boiling alcohol yields di-(6-amino-2 : 4-dihydroxypyrimidin-5-yl) disulphide, identical with the material obtained by interaction of 6-amino-5-bromouracil with sodium disulphide, and a small quantity of 6-amino-2 : 4-dihydroxypyrimidin-5-yl purin-6-yl sulphide (I).


(I)

Similarly, 6-amino-5-bromo-1-methyluracil yielded the corresponding pyrimidinyl disulphide, but it was impossible to isolate any unsymmetrical monosulphide. The formation of the pyrimidinyl disulphides in these reactions is believed to result from the breakdown of the unsymmetrical monosulphide (as I) in which the $C_{(6)}$-atom of the purinyl residue is part of a thioamide system. Such a system would be expected to undergo fission at the $C_{(6)}$–S bond with the formation of a mercaptopyrimidine which would be subsequently converted into a disulphide. Owing to the difficulty of resolving the complex mixture of purines and pyrimidines, it has not been possible to identify with certainty the presence amongst the reaction products of hypoxanthine which would be expected according to the above scheme. However, paper chromatography of the mixture does not exclude its presence, and brief treatment of the pure monosulphide (I) with alkali results in the appearance of a polarographic wave characteristic of disulphides. No such wave is produced on similar treatment of 6-mercaptopurine.

All the disulphides discussed now and in Part I exhibited a unique set of polarographic waves, consisting of two small steps followed by a large reduction wave,[10] and the pattern could be used for identification purposes.

Di-(2 : 4-dihydroxy-6-methylpyrimidin-5-yl) disulphide was used as reference, and a quantitative study was made of the most prominent reduction wave which is also the one at the most negative potential. The value of $E_{\frac{1}{4}}$ for this wave is −0·58 v against the saturated calomel electrode. It is diffusion-controlled in the range of concentration 10^{-3} to 10^{-4} molar (N/10 sodium hydroxide) since the wave-height is proportional to the concentration and to the ratio of the square roots of two heights of the mercury reservoir in accordance with the Ilkovic equation.

After twelve hours, alkaline solutions of the material show an approximately 5% drop in step-height and a drift in the position of the wave towards more positive reduction potential. This effect is most pronounced with di-(6-amino-2 : 4-dihydroxy-1-methylpyrimidin-5-yl) disulphide and less with the disulphides derived from barbituric acid and 6-aminouracil in descending order. It is believed to be due to the formation of a complex by the thiol at the surface of the mercury.

The other pyrimidinyl disulphides behave similarly to the reference in having half-wave potentials in the region −0·5 to −0·6 v against the anodic mercury pool. These waves are preceded by two smaller steps which, for di-(2 : 4-dihydroxy-6-methylpyrimidin-5-yl) disulphide are at $E_{\frac{1}{4}}$ −0·05 and −0·25 v, respectively, against the saturated calomel electrode. The first, which is often accompanied by a maximum, represents an oxidation and has been observed with a number of pyrimidines which contain no disulphide linkage : the second is not diffusion-controlled but varies irregularly with concentration and time. The nature of these waves will be discussed elsewhere.

Experimental

M. p.s are corrected.

Di-(6-amino-2 : 4-dihydroxypyrimidin-5-yl) Disulphide.—Sodium disulphide [prepared from sodium sulphide nonahydrate (2·32 g.) and sulphur (0·28 g.) [11]] in hot 95% ethanol (150 c.c.) was added slowly to a stirred solution of 6-amino-5-bromouracil (1·65 g.) in boiling 95% ethanol (4·8 l.). The solution became dark green, quickly fading to pale yellow, and was refluxed for

[10] Cf. Karchmer and Walker, *Analyt. Chem.*, 1954, **26**, 271.

[11] Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green and Co., London 1941, Vol. II, p. 632.

8 hr. The precipitate was collected after a further 12 hr. at room temperature, washed repeatedly with ethanol and then ether, and dried. It was dissolved in 0·1N-sodium hydroxide (15 c.c.), and the filtered solution (charcoal) brought to pH 2 by addition of N-hydrochloric acid. The *di-(6-amino-2 : 4-dihydroxypyrimidin-5-yl) disulphide* (1·84 g.) was collected, washed, and dried as before (Found : C, 30·2; H, 2·8. $C_8H_6O_4N_4S_2$ requires C, 30·4; H, 2·5%). It does not melt below 350°, and is sparingly soluble in water and ethanol and insoluble in less polar solvents. Light absorption : $\lambda_{max.}$ 269 and 335 mμ ($\log_{10} \varepsilon_{max.}$ 4·33 and 3·66, respectively); $\lambda_{min.}$ 247 and 306 mμ (0·1N-sodium hydroxide). The compound exhibited an oxidation wave ($E_{\frac{1}{2}}$ −0·05 to −0·1 v) and reduction waves ($E_{\frac{1}{2}}$ −0·32 and −0·52 v) at the dropping-mercury electrode. The crystals exhibit parallel extinction under the polarising microscope. Addition of ethanol to an alkaline solution yields a yellow crystalline disodium salt which shows oblique extinction (average value 51·7°).

6-Amino-5-bromo-1-methyluracil and 5 : 5-Dibromohexahydro-6-imino-1-methyl-2 : 4-dioxopyrimidine.—Bromine (2 c.c.) was added dropwise, with stirring, to a suspension of 6-amino-1-methyluracil (5·6 g.) in water (75 c.c.). Stirring was continued at room temperature for 12 hr. and the solid was then collected, washed with cold water, dried in air, and triturated three times with 95% ethanol (total, 200 c.c.). The residual *6-amino-5-bromo-1-methyluracil* (2 g.) separated from hot water in birefringent crystals showing oblique extinction between crossed Nicols (average value 42°), m. p. 278—280° (Found : C, 27·6; H, 2·85. $C_5H_6O_2N_3Br$ requires C, 27·2; H, 2·7%). Light absorption : $\lambda_{max.}$ 225 and 278 mμ ($\log_{10} \varepsilon_{max.}$ 3·73 and 4·2, respectively); $\lambda_{min.}$ 217 and 244 mμ. A further small quantity of the material slowly separated. The filtrate was concentrated to dryness under reduced pressure. The residual glassy *5 : 5-dibromohexahydro-6-imino-1-methyl-2 : 4-dioxopyrimidine* crystallised, on the addition of water, and separated from 30% ethanol in prisms (2·8 g.) which sublimed at 100—101° (Found, in material dried at 20°/18 mm. : C, 19·15; H, 1·8. $C_5H_5O_2N_3Br_2,\frac{1}{2}H_2O$ requires C, 19·4; H, 1·9%). They show parallel extinction when observed under the polarising microscope. The mono- and di-bromo-compounds are readily distinguished by the optical properties of the crystals. The use of a large excess of bromine results exclusively in the formation of the dibromo-compound. Silver bromide is produced by warming the 5 : 5-dibromohexahydro-6-imino-1-methyl-2 : 4-dioxopyrimidine with aqueous silver nitrate, but no test for halide ion is obtained in the cold. This behaviour is similar to that recorded for 5 : 5-dibromohexahydro-6-hydroxy-2 : 4-dioxopyrimidine by Wheeler and Johnson.[13]

Di(hexahydro-6-imino-1-methyl-2 : 4-dioxopyrimidin-5-yl) Disulphide.—6-Amino-5-bromo-1-methyluracil (0·44 g.) in 95% ethanol (200 c.c.) was treated with a 15% solution of sodium disulphide in 95% ethanol (150 c.c.) as in the preparation of di-(6-amino-2 : 4-dihydroxypyrimidin-5-yl) disulphide. The *product* (0·51 g.) formed long acicular crystals which did not melt below 350° and showed parallel extinction under the polarising microscope (Found : C, 35·1; H, 3·8. $C_{10}H_{12}O_4N_6S_2$ requires C, 34·9; H, 3·5%). Light absorption : $\lambda_{max.}$ 267 and 339 mμ ($\log_{10} \varepsilon_{max.}$ 4·29 and 3·60, respectively); $\lambda_{min.}$ 242 and 308 mμ. The compound showed an oxidation wave ($E_{\frac{1}{2}}$ −0·27 and −0·55 v) at the dropping-mercury electrode.

5-Amidinothiohexahydro-6-imino-1-methyl-2 : 4-dioxopyrimidine.—Thiourea (0·065 g.) in ethanol (15 c.c.) was added gradually to 5 : 5-dibromohexahydro-6-imino-1-methyl-2 : 4-dioxopyrimidine (0·34 g.) in ethanol (15 c.c.), and the mixture refluxed for 1 hr., and then set aside at room temperature overnight. The microcrystalline *product* was collected, washed with ethanol and then ether, and recrystallised from 50% ethanol. The material sublimed at *ca.* 180°, forming thick prisms which did not melt below 350° and showed parallel extinction under the polarising microscope (Found : C, 30·35; H, 4·7. $C_6H_9O_2N_5S,H_2O$ requires C, 30·9; H, 4·7%). Treatment of an equivalent of 6-amino-5-bromo-3-methyluracil in the same way yielded an identical product.

Interaction of 6-Amino-5-bromouracil and 6-Mercaptopurine.—6-Mercaptopurine (0·155 g.) in warm 95% ethanol (100 c.c.) was added to a stirred boiling solution of 6-amino-5-bromouracil (0·2 g.) in 95% ethanol (500 c.c.). The solution was refluxed for 24 hr., a precipitate gradually appearing. The volume of the suspension was reduced to 300 c.c. by distillation of the ethanol; the remainder was cooled to room temperature, and di-(6-amino-2 : 4-dihydroxypyrimidin-5-yl) disulphide (0·07 g.) was collected and washed with ethanol and with ether. It was purified as described above (Found : C, 30·55; H, 2·5. Calc. for $C_8H_6O_4N_4S_2$: C, 30·4; H, 2·5%). The compound had the same ultraviolet absorption spectrum and exhibited the same polarographic behaviour as that recorded above. The filtrate from this material was concentrated to 100 c.c.,

[13] Wheeler and Johnson, *J. Biol. Chem.*, 1907, **3**, 187.

and *6-amino-2 : 4-dihydroxypyrimidin-5-yl purin-6-yl sulphide* (0·022 g.) slowly separated and was collected and purified by acidification of a cold solution in N-sodium hydroxide (Found : C, 37·4; H, 3·0; S, 11·3. $C_9H_7O_2N_7S,0·5H_2O$ requires C, 37·8; H, 2·8; S, 11·2%). Light absorption : $\lambda_{max.}$ 268 mμ; $\lambda_{min.}$ 245 mμ ($\log_{10}\varepsilon_{max.}$ 4·19; $\log_{10}\varepsilon_{min.}$ 3·0). The material did not melt below 350° and gave no polarographic reduction wave. It formed a yellow crystalline hydrobromide which was precipitated from an alcoholic solution by addition of ether, and which was reconverted into the free base by addition of sodium hydroxide solution.

Interaction of 6-Amino-5-bromo-1-methyluracil and 6-Mercaptopurine.—6-Mercaptopurine (0·152 g.) and 6-amino-5-bromo-1-methyluracil (0·22 g.) were refluxed in ethanol (150 c.c.) and di(hexahydro-6-imino-1-methyl-2 : 4-dioxopyrimidin-5-yl) disulphide (0·13 g.) was isolated as described in the previous experiment (Found : S, 19·4; N, 23·3. Calc. for $C_{10}H_{12}O_4N_6S_2$: S, 18·6; N, 24·1%). It had the same ultraviolet absorption spectrum and exhibited the same polarographic behaviour as recorded above. Concentration of the mother liquors yielded only a mixture from which no pure monosulphide could be isolated.

All polarographic measurements were made with a Tinsley pen-recording polarograph, Mark 15. Fresh solutions (10^{-4} molar) of di-(2 : 4-dihydroxy-6-methylpyrimidin-5-yl) disulphide in 0·1N-potassium hydroxide (Polaritan grade) were used as standards and measurements were made with two heights of the mercury reservoir (36 cm. and 64 cm.), the standard calomel half-cell being used as the reference anode. Measurements with other pyrimidinyl disulphides were made against the anodic mercury pool, to which the half-wave potentials are referred.

The authors express their indebtedness to Mrs. B. Lamb of the Tinsley Instrument Company for helpful discussions, to Dr. Foster of the Wellcome Foundation for the gift of 6-mercaptopurine, and to the British Empire Cancer Campaign for financial support.

THE UNIVERSITY, MANCHESTER, 13. [*Received, October 13th*, 1955.]

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194. *Nitramines and Nitramides. Part X.* The Formation of Alkyl Cations during Acid-catalysed Decomposition : Evidence from (+)-sec.-Butylnitramine and O-Methyl-N-neopentylnitramine.*

By PETER BRUCK, I. N. DENTON, and ALEX. H. LAMBERTON.

(+)-*sec.*-Butylnitramine has been prepared : on decomposition in aqueous mineral acids the optical activity was almost wholly destroyed. A similar decomposition of *O*-methyl-*N*-*neo*pentylnitramine, in the presence of an oxidising agent, yielded a solution from which acetone—an oxidation product of *tert.*-pentyl alcohol—was isolated as the 2 : 4-dinitrophenylhydrazone.

The resolution of *sec.*-butylamine is improved.

IN earlier papers [1,2] of this series the production of alkyl cations during acid-catalysed decomposition of primary nitramines, and of *ON*-dialkylnitramines, has been postulated mainly on the evidence of the formation of alkyl chlorides. Whilst formation of alkyl chlorides shows that at least some alkyl cations have been produced, non-formation of the chlorides does not disprove production of the cations. Two factors are involved in the formation of RCl from $R{\cdot}NH{\cdot}NO_2$: the production of R^+, and its behaviour in its natal environment. It was therefore decided to apply standard methods for the recognition of alkyl cations to the decomposition of two suitable nitramines. In both cases the results were positive, though by the test of halide formation *sec.*-butylnitramine and *O*-methyl-*N*-*neo*pentylnitramine had given little or no indication of ion formation.

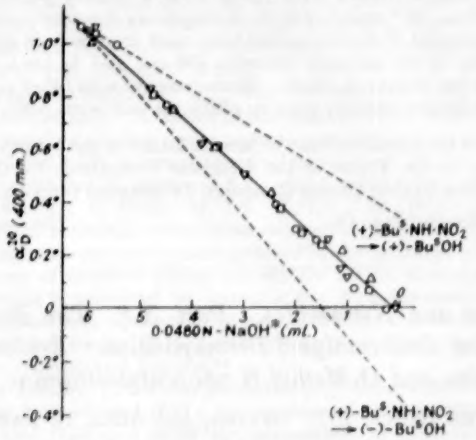
When (+)-*sec.*-butylnitramine was heated in dilute hydrochloric or sulphuric acid the observed rotation fell and, within experimental error, the fall in rotation and the fall in acidity (due to the removal of $Bu^s{\cdot}NH{\cdot}NO_2$) were concurrent. The final values of observed rotation were close to zero, with a slight bias (confirmed by a later experiment) in favour

* Part IX, *J.*, 1955, 3997.

[1] Barrott, Denton, and Lamberton, *J.*, 1953, 1998.
[2] Bruck and Lamberton, *J.*, 1955, 3997.

of negative rotation. The results are best exhibited graphically: the Figure shows a plot of observed rotations against volumes of standard alkali. The broken lines indicate the rotations which would have resulted from the conversion of active *sec.*-butylnitramine into active forms of *sec.*-butyl alcohol, and control experiments have shown that racemisation and volatilisation of *sec.*-butyl alcohol would be unlikely to give a loss of more than 0·03° (runs I—III) or 0·10° (run IV) in optical activity. In a recent paper [3] oxygen exchange and racemisation of *sec.*-butyl alcohol have been correlated on the basis of the incipient formation of a carbonium ion, which reacts with a water molecule before the shielding influence of the original oxygen atom has been withdrawn. Though the nitramine decomposition is presumably similar in some respects, it differs in that the remainder of the molecule has apparently little shielding effect upon the butyl cation.

Relation between rotation and acidity during decomposition of (+)-sec.-butylnitramine at 84°.



△ *Run* I: 592 *mg. of nitramine and* 50 *ml. of* 0·1027M-HCl.
▽ *Run* II: 595 *mg. of nitramine and* 50 *ml. of* 0·1027M-HCl.
□ *Run* III: 594 *mg. of nitramine and* 50 *ml. of* 0·099M-H_2SO_4.
○ *Run* IV: 593 *mg. of nitramine and* 50 *ml. of* 0·01M-H_2SO_4.

* The volume of sodium hydroxide is the excess in titre of a 3 ml. aliquot portion over the titre (of 3 ml.) of the acid used to make up the solution. (As the presence of decomposition products must very slightly lower the concentration of the acid, the final value, at complete decomposition, can be negative on this scale—if the solution has not been concentrated by evaporation. The final values were expected to be between zero and −0·1 ml.; and the lines have been drawn to terminate at −0·05 ml.)

The *neo*pentyl cation, if formed in the decomposition of *O*-methyl-*N*-*neo*pentylnitramine, will rearrange and yield *tert.*-pentyl alcohol by reaction with water. To distinguish *tert.*-pentyl alcohol from *neo*pentyl alcohol in dilute aqueous solution would be difficult: instead, *O*-methyl-*N*-*neo*pentylnitramine was decomposed by 20% sulphuric acid in the presence of dichromate as an oxidising agent. After removal of the excess of oxidant, acetone was isolated as the 2 : 4-dinitrophenylhydrazone. Acetone is a known product of the dichromate oxidation of *tert.*-pentyl alcohol,[4] whilst oxidation of *neo*pentyl alcohol yields trimethylacetaldehyde, trimethylacetic acid, and methyl *iso*propyl ketone.[5] The methylbutenes ($Me_2C{:}CHMe$ and $CH_2{:}CEtMe$) derived from the rearranged cation could act as sources of acetone and of other carbonyl compounds, but not of those materials typical of the oxidation of *neo*pentyl alcohol.

[3] Bunton, Konasiewicz, and Llewellyn, *J.*, 1955, **604**.
[4] Wischnegradski, *Annalen*, 1878, **190**, 355.
[5] Samec, *ibid.*, 1907, **351**, 256; Daniloff and Danilova, *Ber.*, 1926, **59**, 377; Conant, Webb, and Mendum, *J. Amer. Chem. Soc.*, 1929, **51**, 1246; Takagi and Sakaguti, *J. Pharm Soc. Japan*, 1938, **58**, 701.

Experimental

Resolution of sec.-*Butylamine*: *Method of Polarimetric Control.*—Like previous workers [6,7,8] we employed the amine hydrogen tartrates. To use the amine economically, we first removed some (+)-amine (+)-tartrate, then set the slightly lævorotatory residual amine free by treatment of the mother-liquors with sodium hydroxide, and used (−)-tartaric acid to obtain the (−)(−)-salt. When this had been removed, the amine was again liberated, and a second batch of (+)(+)-salt prepared. This procedure was facilitated by polarimetric control, which cannot be direct, since the diastereoisomers from one form of tartaric acid differ only slightly (see below) in rotation. A sample (0·2 g.) of a crop containing the (+)- and (−)-amine in unknown proportions was shaken with 2N-sodium hydroxide (5 ml.) and benzoyl chloride (0·3 ml.). Excess of benzoyl chloride was removed by twice warming the suspension until the crude benzoyl derivative melted, and shaking until solidification occurred. The mixed (+)- and (−)-benzoyl derivatives were extracted with ether (2 × 5 ml.); and the extract was washed with water (3 × 2 ml.), dried (Na_2SO_4), filtered by gravity through a (fluted) hardened filter paper, and evaporated (on the steam-bath, and finally in a vacuum-desiccator), to yield *ca.* 100 mg. of mixed benzamides. Simple precautions were taken to exclude dust. The resolution, which requires about four crystallisations from weights of water rather less than those of the salts, is complete when the benzoyl derivative so produced has $[\alpha]_D^{19-22}$ +31·0° ± 0·2° (*c* 4—5 in EtOH). Repeated crystallisation of a larger sample of the derivative from toluene yielded needles of constant m. p. (95°) and rotation ($[\alpha]_D^{19}$ +31·0°, *c* 4·81 in EtOH): Pope and Gibson [9] gave m. p. 92° and $[\alpha]_D^{20}$ +30·7° (*c* 1·00 in EtOH).

Alcohol may be used to wash the crops, but was an unsatisfactory solvent for crystallisation: the degree of resolution was poor. A few, and unsuccessful, attempts were made to use the pure (+)(+)- and (−)(−)-salts to seed solutions containing both forms of acid and amine. We found passage through a column of "Zeo-karb 225" to be a convenient method of preparing (−)-tartaric acid from sodium ammonium (−)-tartrate, or of recovering (−)-tartaric acid from solutions of disodium (−)-tartrate in aqueous sodium hydroxide.

The active amines were distilled, through a short column, from samples of the pure salts treated with an excess of 40% sodium hydroxide. After drying with solid potassium hydroxide, but without further distillation, these had d_4^{20} 0·731, $[\alpha]_D^{20}$ +7·48°; and d_4^{19} 0·728, $[\alpha]_D^{19}$ −7·64°. Thomé [6] gave d_4^{20} 0·724, $[\alpha]_D^{20}$ +7·44°, whilst Leithe [8] gave $[\alpha]_D^{15}$ +7·80°.

Diastereoisomeric Salts of sec.-*Butylamine with* (+)-*Tartaric Acid.*—(+)-*sec.*-Butylammonium hydrogen (+)-tartrate crystallised from water as slender prisms of the monohydrate, m. p. 96°, $[\alpha]_D^{21}$ +16·8° (*c* 2·8 or 4·8 in H_2O) (Found: C, 40·2, 39·9; H, 7·8, 7·7. Calc. for $C_8H_{17}O_6N,H_2O$: C, 39·8; H, 7·9%). The water of hydration was retained for 18 hr. over potassium hydroxide at 15 mm., but the anhydrous salt was obtained as plates, m. p. 139—140°, $[\alpha]_D^{21}$ +18·1° (*c* 10·8 in H_2O), on crystallisation from alcohol and drying, finally over phosphoric oxide at 80°/0·1 mm. (Found: C, 43·5; H, 7·7. Calc. for $C_8H_{17}O_6N$: C, 43·0; H, 7·6%). Thomé [6] gave analyses of the monohydrate, but no m. p.; Leithe [8] gave m. p. (98—99° and 146—147°) but no analyses.

The more soluble (−)-*sec.*-butylammonium hydrogen (+)-tartrate was prepared from the pure (−)-amine and tartaric acid. Crystallisation from water yielded material of indeterminate constitution, but the *monohydrate* was obtained as needles by crystallisation from ethanol–water (4 : 1 by vol.) and 7 days' exposure to the atmosphere. The material had m. p. 85°, $[\alpha]_D^{21}$ +17·8° (*c* 2·8 in H_2O) (Found: C, 40·1; H, 7·9. $C_8H_{17}O_6N,H_2O$ requires C, 39·8; H, 7·9%). The *anhydrous salt*, obtained by crystallisation from ethanol and drying, finally over phosphoric oxide at 80°/0·1 mm., had m. p. 138—139°, $[\alpha]_D^{20}$ +19·8° (*c* 9·9 in H_2O) (Found: C, 43·0; H, 7·3. $C_8H_{17}O_6N$ requires C, 43·0; H, 7·6%).

The rotations and m. p.s of the anhydrous salts are subject to some uncertainty, as water is rapidly absorbed from the atmosphere. The rotations of the monohydrates were determined in a 400 mm. polarimeter tube.

(+)-sec.-*Butylnitramine.*—The amine was converted into the nitramine by standard methods.[10,11] The intermediate (+)-*sec.*-butylurethane had d_4^{21} 0·945, $[\alpha]_D^{21}$ +19·3°, whilst the intermediate (+)-*sec.*-butylnitrourethane had d_4^{19} 1·098 and $[\alpha]_D^{19}$ +10·2°. (+)-sec.-*Butylnitramine*, b. p. 101°/10 mm. (Found: C, 40·9; H, 8·7. $C_4H_{10}O_2N_2$ requires C, 40·7; H, 8·5%).

[6] Thomé, *Ber.*, 1903, **36**, 582.
[7] Fleury-Larsonneau, *Bull. Soc. chim. France*, 1939, **6**, 1576.
[8] Leithe, *Ber.*, 1930, **63**, 804.
[9] Pope and Gibson, *J.*, 1912, **101**, 1706.
[10] Denton and Lamberton, *J.*, 1955, 1655.
[11] Curry and Mason, *J. Amer. Chem. Soc.*, 1951, **73**, 5042.

had α_D (100 mm.) +45·1°, 44·9°, and 44·6° at, respectively, 18°, 19°, and 20°, d_4^{20} 1·061, and $[\alpha]_D^{20}$ +42·1°. The following rotations were observed in solution : $[\alpha]_D^{21}$ +28° (*c* 0·47 in H_2O), +40° (*c* 4·1 in EtOH), $[\alpha]_D^{20}$ +35° (*c* 4·2 in $CHCl_3$), +39° (*c* 3·6 in $Ph{\cdot}NO_2$), $[\alpha]_D^{21}$ +49° (*c* 0·44 in 0·0915M-NaOH, equiv. to Na salt in 0·042M-NaOH). The solution of the sodium salt had unchanged rotation after 2 weeks at room temperature.

Determination of Alkyl Chloride formed by Decomposition in 1·0M-*Hydrochloric Acid.*—The method has been reported.[2] In two experiments, (±)-*sec.*-butylnitramine showed halide formation of 3·0, 3·8% by acidimetry, and 2·8, 3·9% by determination of chloride ion. *O*-Methyl-*N*-*neo*pentylnitramine gave no indication of halide formation.[2]

Decomposition of (+)-sec.-*Butylnitramine.*—The solutions (see Figure for compositions) were heated, under a ground-glass reflux condenser, in a 100 ml. flask immersed to the neck in the thermostat. At suitable intervals the flask was removed and the contents were cooled rapidly to 20°; the rotation was observed in a 400 mm. tube, and the acidity found by titration of a 3 ml. sample. The polarimetric solution was returned to the flask, and heating re-commenced. The sample of nitramine used was of 78% optical purity, having α_D^{16} (100 mm.) +35·1°. The rate of decomposition was in agreement with earlier measurements [10] of greater precision; half-life times were about 95 min. for runs I—III, and 12 hr. for run IV. Final observations were made after, respectively, *ca.* 24 hr., 1023 min., 1146 min., and 90 hr. of heating. At these (final) times the residual nitramine should be negligible, but the alkali titres were higher than expected. These discrepancies, which may have arisen from evaporation, or other causes, were in all cases less than 0·3 ml., and it has been thought best to make no attempt at " correction " : the Figure is based simply on the observed values. The end-points of the broken lines are uncertain to perhaps ±0·03°; their calculation involves the optical purity of the nitramine, also the rotation (in dilute acid) and optical purity of the *sec.*-butyl alcohol prepared by us; curiously, no value of the rotation of (+)-*sec.*-butyl alcohol in water appears to exist in the literature. We found that a sample of 93·4% optical purity [12] [dried by distillation from barium oxide : α_D^{20} +10·21° (100 mm.)] had $[\alpha]_D^{20}$ +13·5° (*c* 2·61 or 0·75 in H_2O, or 0·75 in 0·11M-HCl). From this, the rotation of the pure (+)-isomer is $[\alpha]_D^{20}$ +14·5° in dilute aqueous solutions.

Racemisation of sec.-*Butyl Alcohol.*—The results of Bunton *et al.*,[3] and our own experiments in sealed tubes, show that racemisation of the alcohol could not cause significant loss of optical activity during the decomposition of *sec.*-butylnitramine. A more likely source of error would be volatilisation of the alcohol. A sample of 70—75% optical purity was prepared,[13] and solutions (of similar molarity to those of the nitramine) were treated as described for the decomposition of *sec.*-butylnitramine. A slow loss of activity, due to volatilisation and racemisation, was observed; and the results, expressed as the time for the loss of half the activity, were between 150 and 300 hr. for hydrochloric acid (0·11 or 0·002M), or for sulphuric acid (0·10 or 0·01M). In the decomposition of *sec.*-butylnitramine the rate of volatilisation may increase on account of the evolution of nitrous oxide, but we believe the figures we have given (0·03° for 24 hr., and 0·1° for 90 hr.) to be a generous estimate of the losses which could thus result; and also, if the changes in rotation shown in the Figure were due to volatilisation or racemisation, it seems most unlikely that they would be—as in fact they are—related linearly to the changes in acid titre.

Confirmatory Experiments in Sealed Tubes.—A sample of pure (+)-*sec.*-butylnitramine (236·8 mg., 2·01 mmole) was made up to 20 ml. with 0·110M-hydrochloric acid, and heated in a sealed tube for 16 hr. at 86—88°. The residual nitramine, by acidimetry, was less than 1%. The observed rotations, α_D^{23} (400 mm.), were initially +1·265° and finally −0·025°. The reality of the small negative rotation was confirmed by distillation of the residual solution available (16—17 ml.) through a short column. A first fraction of rather less than 1 ml. was collected, and found to have α_D^{23} (100 mm.) −0·11°. Quantitative production of (−)-*sec.*-butyl alcohol would have given a rotation of about −0·43° in the 400 mm. tube, compared with the observed value of −0·025°. A sample of partially resolved *sec.*-butyl alcohol (143·8 mg., 1·94 mmole) was made up to 20 ml. with the same acid, and heated similarly and simultaneously in the same furnace. The rotation, α_D^{23} (400 mm.), was practically unaltered (+0·34° ⟶ +0·325°). A second sample of alcohol (141·1 mg.), made up to 20 ml. with the same acid, gave rotations of +0·32° and +0·31° before and after heating at 86—90° for 17 hr. Samples of the alcohol in, respectively, 0·110M-hydrochloric acid and 0·01M-sulphuric acid were heated simultaneously for 87 hr. at 86—90° : the rotations, α_D^{21-22} (400 mm.) changed only from +0·31° to +0·30°, and from +0·34°

[12] Pickard and Kenyon, *J.*, 1913, **103**, 1941.
[13] Ingersoll, " Organic Reactions," Wiley and Sons, New York, 1944, Vol. II, p. 403.

to +0·33°. These changes cannot be considered of quantitative significance, but show that the rate of racemisation is very small.

Decomposition of O-*Methyl*-N-*neopentylnitramine in an Oxidising Medium.*—O-Methyl-N-*neo*pentylnitramine (0·21 g.) was heated under reflux for 2 hr. on the steam-bath with 0·5N-potassium dichromate (40 ml.) and concentrated sulphuric acid (5 ml.). After cooling, the excess of oxidant was removed by the addition of sodium sulphite (2 g.); the resultant solution was added to a saturated aqueous solution of 2 : 4-dinitrophenylhydrazine hydrochloride (50 ml.), and the whole set aside overnight at 0°. If sodium sulphite was not added, oxidation of the hydrazine gave 2 : 4-dinitrophenol. Acetone 2 : 4-dinitrophenylhydrazone (250 mg., crude) was collected and identified, after two crystallisations from acetic acid–water, by m. p. (124°) and mixed m. p. (Found : C, 45·2; H, 4·3. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·2%). The m. p. was depressed to 90° by mixture with the 2 : 4-dinitrophenylhydrazone of methyl *iso*propyl ketone (m. p. 120°).

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195. *The Crystal Structure of the Monoclinic Modification of* 1 : 2-5 : 6-*Dibenzanthracene. A Quantitative X-Ray Investigation.*

By J. Monteath Robertson and J. G. White.

The crystal and molecular structure of the monoclinic modification of 1 : 2-5 : 6-dibenzanthracene has been determined, and the co-ordinates of all the carbon atoms are given. The space group is $P2_1$, and the molecule does not display any crystallographic symmetry. The final results, however, indicate a planar structure with the molecular symmetry required by the chemical formula. All the bond lengths have been evaluated and agree well with those obtained from a study of the orthorhombic modification, already described. When the most reliable bond-length measurements are selected from these two independent crystal-structure determinations, excellent agreement is obtained with the theoretical calculations of Vroelant and Daudel.

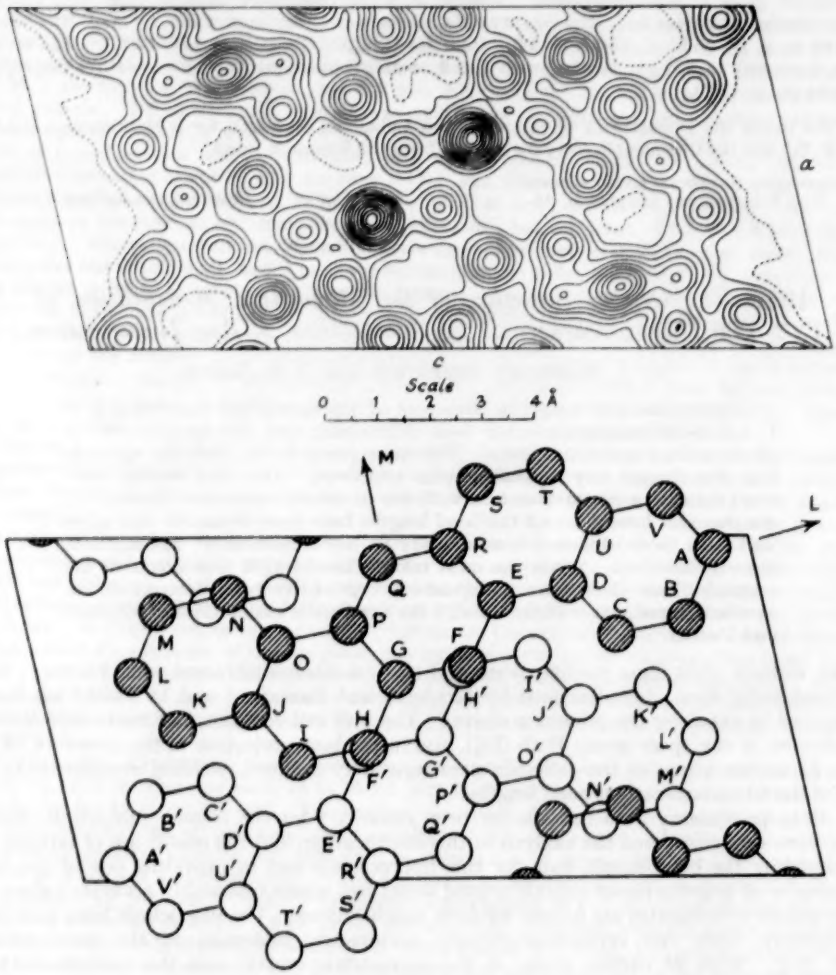
Two distinct crystalline modifications of 1 : 2-5 : 6-dibenzanthracene are known. The orthorhombic form, first described by Krishnan and Banerjee [1] and by Iball,[2] has been analysed in detail by the present authors.[3] The unit cell contains four centro-symmetric molecules in the space group Pcab (D_{2h}^{15}), and in the best projection of the structure 18 of the 22 carbon atoms in the molecule were separately resolved, yielding measurements of 18 of the 26 carbon–carbon bond lengths.

Only preliminary data have so far been recorded [4] for the second, monoclinic, form. We have now completed the analysis of this modification, and the results are of interest in completing the bond-length data for this hydrocarbon and in providing one of the few examples of polymorphous organic crystal structures where reasonably accurate values of the atomic co-ordinates are known for both modifications. The monoclinic form is of low symmetry, with two crystallographically asymmetric molecules in the space group $P2_1$ (C_2^2). With 22 carbon atoms in the asymmetric crystal unit the analysis is thus considerably more complex than for the orthorhombic form. But the final results yield a clear projection of the molecule, with 18 of the 22 carbon atoms resolved (Fig. 1). By assuming a centre of symmetry in the molecule (as demanded by the chemical structure but not required crystallographically) co-ordinates can be assigned to the unresolved atoms

[1] Krishnan and S. Banerjee, *Z. Krist.*, 1935, **91**, 170.
[2] Iball, *Nature*, 1936, **137**, 361.
[3] J. M. Robertson and White, *J.*, 1947, 1001.
[4] Iball and J. M. Robertson, *Nature*, 1933, **132**, 750.

and all the bond lengths ascertained. The information finally obtained is thus more complete than that derived from the orthorhombic modification, and is discussed below. As the present work employs only two-dimensional Fourier methods the accuracy is not particularly high and the probable errors in bond length are about $\pm 0{\cdot}02$ Å. The main

FIG. 1. *Projection along the* b *axis on* (010). *The molecules are inclined at about* 22° *to the projection plane. Each contour line represents a density increment of one electron per* Å^3, *the one-electron line being broken.*



features of the bond-length variations, however, are found to agree well with those obtained from the orthorhombic modification. It seems likely that more accurate results will only be possible by the use of three-dimensional methods, and the present analysis should provide the necessary first approximation for any such further refinement.

Crystal Data.—1 : 2-5 : 6-Dibenzanthracene, $C_{22}H_{14}$; M, 278·3; m. p. 267·5°; d, calc. 1·288, found 1·282; monoclinic, $a = 6{\cdot}59$, $b = 7{\cdot}84$, $c = 14{\cdot}17$ Å, $\beta = 103{\cdot}5°$. Absent spectra,

(0*k*0) when *k* is odd. Space group, $P2_1$ (C_2^2) or $P2_1/m$ (C_{2h}^2). $P2_1$ is indicated by this analysis. Two molecules per unit cell. No molecular symmetry required. Volume of the unit cell, 712 Å^3. Absorption coefficient for $\lambda = 1{\cdot}54$ Å, $\mu = 6{\cdot}74$ cm.$^{-1}$. Total number of electrons per unit cell = F(000) = 292.

The crystals were obtained from alcohol in the form of thin irregular plates, with only (001) prominently developed. The maximum thickness obtained (along *c*) was only about 0·1 mm., but it was possible to cut small needle-shaped specimens suitable for *X*-ray rotation photographs about the *a* and the *b* axis. Fairly complete intensity data were therefore collected for the (0*kl*) and (*h*0*l*) zones.

Structure Analysis.—Packing considerations show that the space group of higher symmetry, $P2_1/m$, is most improbable unless the molecules lie entirely in the (010) plane. However, evidence from magnetic-susceptibility measurements and that from *X*-ray intensities both show that the molecular planes are inclined at a small angle (about 20—25°) to the (010) plane. Space group $P2_1/m$ therefore appears to be excluded, and in what follows we assume the lower symmetry of $P2_1$.

The most outstanding reflection observed is (020) with F value of 159 (possible maximum about 200 at this angle). The situation is evidently similar to that observed in the orthorhombic modification, where the (200) reflection had a correspondingly high intensity. It can be safely assumed that the molecular plane is only inclined at a small angle to (010), and in particular that the long axis of the molecule (*L* in Fig. 1) must lie almost entirely in (010). A measure of the maximum degree of tilt of the other molecular axis (*M*) is obtained from the magnetic measurements due to Krishnan and Banerjee [5] who deduce an angle of about 25° between the molecular plane and (010).

A survey of the higher-order (*h*0*l*) reflections now shows that (00,13), (10$\bar{7}$), (209), (308), (302), (30$\bar{5}$), (30$\bar{1}\bar{1}$), and (60$\bar{3}$) are all strong. In this projection, along the two-fold axis, the structure has an effective centre of symmetry, and by studying the traces of these planes drawn in the projection, as has been described in detail in the analysis of the coronene structure,[6] positions of the molecules can be found which account for these enhancements. The weakness of the large-spacing reflections (100) and (10$\bar{1}$) also provides evidence concerning the overall positions of the two molecules and enable us to locate their centres at approximately $x = 1{\cdot}8$ Å, $z = 0{\cdot}5$ Å from the two-fold axis.

Trial calculations of the structure factors on this basis immediately yielded a considerable measure of agreement with the observed values. The parameters were then refined by a number of successive Fourier syntheses of the (*h*0*l*) structure factors. The final electron-density projection obtained is shown in Fig. 1, and the F values and phase constants of the terms included in this synthesis are given in Table 5.

By averaging certain distances as described more fully below (p. 929) the orientation of the molecule can be calculated on the assumption that the molecular axes *L* and *M* (Figs. 1 and 2) are at right angles and that the molecule is planar. The results are given in Table 1, where χ, ψ, and ω are respectively the angles which the molecular axes *L* and *M*, and their perpendicular *N* make with the *a*, *b*, and *c*′ crystal axes (*c*′ is taken perpendicular to *a* and *b*).

TABLE 1. *Orientation of the molecule in the crystal.*

$\chi_L = 91{\cdot}1°$, $\cos\chi_L = -0{\cdot}0331$;	$\chi_M = 22{\cdot}4°$, $\cos\chi_M = 0{\cdot}9245$;
$\psi_L = 91{\cdot}5°$, $\cos\psi_L = -0{\cdot}0256$;	$\psi_M = 67{\cdot}7°$, $\cos\psi_M = 0{\cdot}3795$;
$\omega_L = 2{\cdot}4°$, $\cos\omega_L = 0{\cdot}9991$;	$\omega_M = 87{\cdot}7°$, $\cos\omega_M = 0{\cdot}0404$;

$\chi_N = 112{\cdot}3°$, $\cos\chi = -0{\cdot}3797$.
$\psi_N = 22{\cdot}3°$, $\cos\psi_N = 0{\cdot}9247$.
$\omega_N = 89{\cdot}2°$, $\cos\omega_N = 0{\cdot}0142$.

In the final electron-density map it will be noted that 18 out of the 22 independent atoms are resolved, although some are rather distorted by proximity to atoms of adjoining molecules. Co-ordinates were next assigned to the resolved atoms on the basis of this

[5] Krishnan and S. Banerjee, *Z. Krist.*, 1935, **91**, 173.
[6] J. M. Robertson and White, *J.*, 1945, 607.

projection and of subsidiary difference syntheses, with allowance for overlap and series-termination effects. These co-ordinates are collected in Table 3 under $X(b)$ and $Z(b)$. Assuming that the molecule is strictly centrosymmetrical we can now obtain an accurate value for the co-ordinates of the molecular centre by taking the mean value of the x and z co-ordinates of the 7 pairs of atoms, A and L, B and M, etc. The co-ordinates of the 18 resolved atoms with respect to the molecular axes L and M can now be readily calculated by taking account of the orientation (Table 1) and the position of the molecular centre. These co-ordinates (in Å) are given in Table 3 under $L(b)$ and $M(b)$, and these figures provide the bond lengths directly.

We may now compare bond lengths between crystallographically independent atoms related by the assumed molecular centre of symmetry. The results are given in Table 2.

TABLE 2. *Bond lengths (in* Å).

AB = 1·44	LM = 1·39	Assumed mean value	= 1·41
AV = 1·40	LK = 1·39	,, ,,	= 1·40
UV = 1·39	KJ = 1·40	,, ,,	= 1·40
DE = 1·40	OP = 1·40	,, ,,	= 1·40
UD = 1·45	OJ = 1·45	,, ,,	= 1·45
PG = 1·43	RE = 1·45	,, ,,	= 1·44

FIG. 2. *Dimensions of the molecule of* 1 : 2-5 : 6-*dibenzanthracene.*

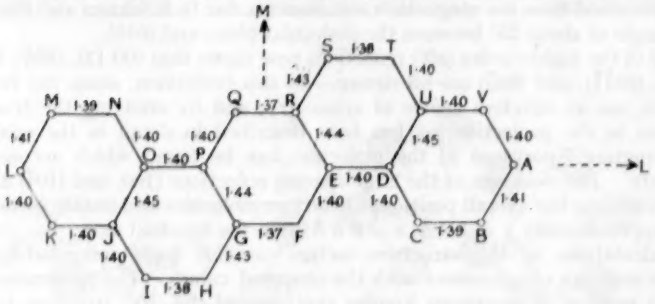


TABLE 3.

Co-ordinates. Origin on two-fold axis. x, y, z are expressed as fractions of the axial lengths, X, Y, Z, L, and M in Å. Space group, $P2_1$. General positions, x, y, z; $\bar{x}, \frac{1}{2}+y, \bar{z}$.

Atom	x	y	z	X (*a*)	X (*b*)	Y (*a*)	Z (*a*)	Z (*b*)	L (*a*)	L (*b*)	M (*a*)	M (*b*)
A	0·457	−0·017	0·447	3·017	3·030	−0·131	6·342	6·365	5·651	5·671	0·035	0·046
B	0·262	−0·073	0·392	1·729	1·712	−0·576	5·563	5·570	4·941	4·946	−1·186	−1·200
C	0·210	−0·072	0·292	1·385	1·385	−0·565	4·139	4·139	3·557	3·557	−1·249	−1·249
D	0·354	−0·012	0·242	2·332	2·340	−0·095	3·435	3·442	2·825	2·830	−0·062	−0·066
E	0·311	−0·007	0·141	2·054	2·040	−0·059	1·999	2·002	1·426	1·428	−0·061	−0·075
F	0·123	−0·061	0·081	0·813	—	−0·478	1·146	—	0·645	—	−1·216	—
G	0·083	−0·056	−0·018	0·548	0·554	−0·436	−0·259	−0·248	−0·725	−0·714	−1·197	−1·193
H	−0·114	−0·112	−0·074	−0·749	—	−0·883	−1·050	—	−1·444	—	−2·426	—
I	−0·152	−0·107	−0·174	−1·007	−1·007	−0·838	−2·465	−2·465	−2·823	−2·823	−2·397	−2·397
J	−0·006	−0·047	−0·223	−0·040	−0·038	−0·365	−3·158	−3·162	−3·544	−3·549	−1·203	−1·200
K	−0·055	−0·044	−0·324	−0·364	−0·360	−0·341	−4·593	−4·592	−4·939	−4·949	−1·237	−1·244
L	0·093	0·017	−0·372	0·615	0·630	0·131	−5·270	−5·254	−5·651	−5·632	−0·035	−0·024
M	0·289	0·073	−0·317	1·903	1·890	0·576	−4·493	−4·490	−4·941	−4·935	1·186	1·172
N	0·341	0·072	−0·217	2·247	—	0·565	−3·069	—	−3·557	—	1·249	—
O	0·197	0·012	−0·167	1·300	1·286	0·095	−2·365	−2·360	−2·825	−2·819	0·062	0·057
P	0·239	0·007	−0·066	1·578	1·570	0·059	−0·929	−0·932	−1·426	−1·423	0·061	0·048
Q	0·427	0·061	−0·005	2·819	2·819	0·478	−0·076	−0·076	−0·645	−0·645	1·216	1·216
R	0·468	0·056	0·094	3·084	3·070	9·436	1·329	1·342	0·725	0·735	1·197	1·201
S	0·664	0·112	0·149	4·381	4·381	0·883	2·120	2·120	1·444	1·444	2·426	2·426
T	0·704	0·107	0·249	4·639	—	0·838	3·535	—	2·823	—	2·397	—
U	0·557	0·047	0·298	3·672	3·674	0·365	4·228	4·222	3·544	3·538	1·203	1·205
V	0·606	0·044	0·399	3·996	3·984	0·341	5·663	5·652	4·939	4·929	1·237	1·230
	Molecular centre,			1·816	—	0	0·535	—	—	—	—	—

These results appear to justify averaging the molecular co-ordinates $L(b)$ and $M(b)$ of Table 3 in pairs where possible (A and L, B and M, etc.), with the advantage that we can now derive all the bond distances in the molecule. The averaged molecular co-ordinates are given under $L(a)$ and $M(a)$ in Table 3, and the crystal co-ordinates obtained from them by combination with the orientation angles are given under $X(a)$, $Y(a)$, and $Z(a)$. The bond lengths finally derived from these co-ordinates are shown in Fig. 2, where the ringed atoms are those separately resolved in Fig. 1.

In Table 4 these bond-length measurements are summarized and compared with those derived from the orthorhombic modification. The results are seen to be in reasonably good agreement. The position of the atom K was very uncertain in the orthorhombic structure, and here the monoclinic results are more reliable, while for the bond lengths EF and FG the orthorhombic results are probably better. The Table gives also the best values derived from a consideration of the merits of both crystal structures.

TABLE 4. *Comparison of bond-length measurements (in* Å*) in monoclinic and orthorhombic dibenzanthracene.*

Bond	Mono-clinic	Ortho-rhombic	Best value	Calc. length [7]	Δ	Bond	Mono-clinic	Ortho-rhombic	Best value	Calc. length [7]	Δ
AB	1·41	1·41	1·41	1·40	0·01	*HI*	1·38	—	1·38	1·38	0·00
BC	1·40	—	1·40	1·39	0·01	*IJ*	1·40	—	1·40	1·42	0·02
CD	1·40	—	1·40	1·41	0·01	*JK*	1·40	1·44 ?	1·40	1·42	0·02
DE	1·40	1·41	1·41	1·44	0·03	*KL*	1·40	1·44 ?	1·40	1·39	0·01
EF	1·40 ?	1·38	1·39	1·41	0·02	*DU*	1·45	1·42	1·44	1·44	0·00
FG	1·37 ?	1·40	1·40	1·41	0·01	*RE*	1·44	1·44	1·44	1·44	0·00
GH	1·43	1·45	1·44	1·42	0·02						

The existence of exceptionally long bonds in the central ring at RE, and at GH and DU appears to be definitely confirmed. It is interesting to note that the distortion of the molecule can be detected quite readily on the electron density map by drawing a straight line through the atoms A, D, and E. This line is parallel to, but does not coincide with, the line through L, O, and P. The situation is exactly similar in the orthorhombic structure, when a line through A, D, and E did not pass through the origin.

In our previous paper [3] we discussed the expected values of the bond lengths from a simple consideration of the double-bond character of each link as assessed from the contributing Kekulé structures. Since that time more exact theoretical calculations of these bond lengths have been made by Vroelant and Daudel [7] and their results are given as " Calc. length " in Table 4. A very good overall agreement with our measurements is reached, the average discrepancy (Δ) being only slightly over 0·01 Å, with a maximum discrepancy of 0·03 Å for the bond DE.

From a consideration of our experimental data, and the agreements obtained between calculated and observed F values, we expect probable errors of about ±0·02 Å for our original directly measured bond lengths. The process of averaging the molecular co-ordinates, and in particular the fact that our final values are now based on two entirely independent crystal structures, will considerably increase the significance of these final results. The agreements obtained with the theoretical calculations are therefore encouraging.

Intermolecular distances have not been calculated in detail, but the closest contacts between atoms of adjacent molecules appear to be of the usual order of 3·5 and 3·6 Å, except between atom S on the standard molecule and O on the nearest rotated molecule, where the unusually small distance of 3·3 Å is observed.

EXPERIMENTAL

Small specimens were cut from the rather irregular plates obtained from alcohol and mounted for rotation, oscillation, and moving-film photographs about the principal crystallographic axes. For the a axis rotations the specimen weighed 0·108 mg. and had a cross section of

[7] Vroelant and R. Daudel, *Bull. Soc. chim. France*, 1949, **16**, 36, 217; *Compt. rend.*, 1949, **228**, 399; Buu-Hoï, R. Daudel, and Vroelant, *Bull. Soc. chim. France*, 1949, **16**, 211.

TABLE 5. *Measured and calculated values of the structure factor.*

hkl	$F_{meas.}$	$F_{calc.}$	$\alpha°_{calc.}$
000	—	292	0
100	9	10	180
200	12	12	180
300	2	7	0
400	< 2	3	180
500	4	6	180
600	< 2	1	180
700	< 2	1	0
800	< 1	0	—
020	159	154	0
040	< 4	16	0
060	12	8	180
001	41	41	0
002	34	34	180
003	15	18	0
004	10	8	180
005	8	8	0
006	11	7	180
007	2	3	0
008	4	4	180
009	< 2	2	180
00,10	4	3	0
00,11	< 2	1	180
00,12	6	6	0
00,13	13	14	0
00,14	2	1	0
00,15	< 2	1	180
10,10	< 2	2	0
109	3	0	—
108	4	4	180
107	7	11	180
106	20	20	0
105	< 1	0	—
104	12	9	180
103	2	1	180
102	8	5	180
101	20	22	0
$10\bar{1}$	4	4	0
$10\bar{2}$	7	1	0
$10\bar{3}$	23	23	0
$10\bar{4}$	4	5	180
$10\bar{5}$	4	5	0
$10\bar{6}$	4	3	180
$10\bar{7}$	34	34	180
$10\bar{8}$	9	10	180
$10\bar{9}$	7	10	180
$10,\bar{1}0$	6	6	180
$10,\bar{1}1$	2	2	0
$10,\bar{1}2$	2	3	0
$10,\bar{1}3$	< 2	0	—
20,16	1	1	180
20,15	< 1	2	180
20,14	< 2	1	180
20,13	< 2	1	180
20,12	4	3	0
20,11	3	4	0
20,10	8	8	0
209	24	24	0
208	2	1	0
207	4	7	180
206	< 2	1	0
205	< 1	0	—
204	3	2	180
203	14	17	0
202	17	18	0
201	29	32	180
$20\bar{1}$	23	25	0
$20\bar{2}$	28	32	0
$20\bar{3}$	9	11	0
$20\bar{4}$	29	28	0
$20\bar{5}$	5	3	0
$20\bar{6}$	2	4	180
$20\bar{7}$	< 1	1	180
$20\bar{8}$	< 2	1	0
$20\bar{9}$	2	0	—
$20,\bar{1}0$	2	4	0
$20,\bar{1}1$	10	5	0
$20,\bar{1}2$	5	6	180
$20,\bar{1}3$	< 2	0	—
30,11	< 2	0	—
30,10	4	2	180
309	9	9	0
308	26	21	0
307	3	5	180
306	3	3	0
305	2	2	180
304	2	1	180
303	7	4	180
302	49	48	180
301	15	13	180
$30\bar{1}$	2	1	0
$30\bar{2}$	1	1	180
$30\bar{3}$	4	3	180
$30\bar{4}$	19	21	0
$30\bar{5}$	30	27	0
$30\bar{6}$	7	9	180
$30\bar{7}$	2	5	0
$30\bar{8}$	2	1	180
$30\bar{9}$	2	2	0
$30,\bar{1}0$	9	9	180
$30,\bar{1}1$	35	33	180
$30,\bar{1}2$	5	3	180
$30,\bar{1}3$	3	4	0
$30,\bar{1}4$	< 2	1	180
40,10	< 2	0	—
409	2	2	0
408	5	4	180
407	< 2	1	0
406	< 2	0	—
405	2	1	180
404	< 2	0	—
403	< 2	2	180
402	3	4	180
401	7	4	180
$40\bar{1}$	8	9	180
$40\bar{2}$	4	1	180
$40\bar{3}$	6	5	180
$40\bar{4}$	2	5	0
$40\bar{5}$	15	14	180
$40\bar{6}$	3	2	180
$40\bar{7}$	< 2	2	0
$40\bar{8}$	< 2	0	—
$40\bar{9}$	< 2	0	—
$40,\bar{1}0$	2	1	0
$40,\bar{1}1$	4	4	180
$40,\bar{1}2$	7	7	180
$40,\bar{1}3$	< 2	0	—
$40,\bar{1}4$	3	4	180
$40,\bar{1}5$	< 2	0	—
507	< 2	2	0
506	2	2	0
505	5	5	0
504	6	8	0
503	2	2	180
502	< 2	2	0
501	3	2	180
$50\bar{1}$	6	3	180
$50\bar{2}$	7	8	180
$50\bar{3}$	3	0	—
$50\bar{4}$	3	2	180
$50\bar{5}$	< 2	2	0
$50\bar{6}$	< 2	1	0
$50\bar{7}$	2	2	0
$50\bar{8}$	4	4	180
$50\bar{9}$	2	2	180
$50,\bar{1}0$	4	5	0
$50,\bar{1}1$	< 2	1	0
605	< 2	0	—
604	2	2	180
603	< 2	0	—
602	< < 2	0	—
601	< < 2	1	0
$60\bar{1}$	2	3	0
$60\bar{2}$	19	16	180
$60\bar{3}$	28	24	180
$60\bar{4}$	8	6	0
$60\bar{5}$	2	0	—
$60\bar{6}$	< 2	1	0
$60\bar{7}$	< 2	1	0
$60\bar{8}$	2	2	180
$60\bar{9}$	4	4	0
$60,\bar{1}0$	< 2	1	0
$60,\bar{1}1$	< < 2	0	—
$60,\bar{1}2$	< < 2	0	—
$60,\bar{1}3$	< 2	1	180
$60,\bar{1}4$	< 1	0	—
$60,\bar{1}5$	2	3	180
703	< 1	2	180
702	2	2	0
701	< 2	1	180
$70\bar{1}$	< < 2	0	—
$70\bar{2}$	< < 2	1	180
$70\bar{3}$	3	2	0
$70\bar{4}$	< < 2	0	—
$70\bar{5}$	< < 2	0	—
$70\bar{6}$	< < 2	1	180
$70\bar{7}$	< 2	1	0
$70\bar{8}$	3	1	180
$70\bar{9}$	3	3	0
$70,\bar{1}0$	< < 1	2	0
801	< 1	0	—
$80\bar{1}$	< < 1	0	—
$80\bar{2}$	< < 1	2	0
$80\bar{3}$	< 1	0	—
$80\bar{4}$	2	2	180
$80\bar{5}$	2	2	180
$80\bar{6}$	2	2	180
$80\bar{7}$	< 1	2	180
011	12	17	152
012	29	25	215
013	14	14	98
014	9	10	288
015	16	15	92
016	49	40	271
017	42	34	269
018	14	12	101
019	< 4	3	134
021	22	16	347
022	23	22	231
023	12	15	353
024	5	7	143
025	7	6	9
026	13	6	137
027	4	8	72
028	7	10	103
029	5	6	84
02,10	< 3	3	341
02,13	8	9	1
031	< 5	9	177
032	19	19	182
033	7	8	93
034	< 4	6	286
035	7	9	88
036	12	15	272

TABLE 5. (*Continued.*)

hkl	$F_{meas.}$	$F_{calc.}$	$\alpha°_{calc.}$	*hkl*	$F_{meas.}$	$F_{calc.}$	$\alpha°_{calc.}$	*hkl*	$F_{meas.}$	$F_{calc.}$	$\alpha°_{calc.}$
037	5	8	265	054	9	5	239	065	<3	1	19
038	<3	2	172	055	<4	3	86	069	7	3	249
043	<4	4	23	05,10	8	6	133	071	<4	3	356
044	7	4	211	061	<3	3	158	072	12	6	4
051	<4	5	347	062	9	4	55	073	<4	6	287
052	10	5	32	063	5	6	162	074	10	5	233
053	5	3	307	064	12	6	235				

0·15 × 0·56 mm. Other specimens employed were of similar size. Cu-$K\alpha$ radiation was used in all the photographic work, and approximate absorption corrections were calculated for a few of the stronger reflections only. The F values were derived by the usual formulæ, and the absolute scale was determined approximately by comparisons made on the two-crystal moving-film spectrometer [8] with previously measured standards. Intensity measurements were made on an integrating photometer, with visual estimations for the weaker spots. Although every care was taken with the measurements, the results are not expected to be particularly accurate owing to the rather thin and badly shaped specimens.

The Fourier calculations were carried out with three-figure strips, the *c* axis intervals being 60ths (0·236 Å), and the *a* axis interval 30ths (0·220 Å). For calculation of the orientation of the molecule, a mean hexagonal radius of 1·41 Å was chosen. The mean measured length of the lines *BV*, *CU*, *ES*, *GQ*, *IO*, and *KM* (see Fig. 1) is found to be 2·258 ± 0·03 Å. Hence

$$\psi_M = \sin^{-1}(2{\cdot}258/2{\cdot}44) = 67{\cdot}7°$$

The mean value of the angles between the lines *VURQM*, *ADEPOL*, *BCGJK*, and the *a* axis gives

$$\tau_{iL} = 91{\cdot}9° \pm 0{\cdot}3°$$

The mean value of the angles between *BV*, *CU*, *ES*, *GQ*, *IO*, *KM*, and the *a* axis gives

$$\tau_{iM} = 2{\cdot}5° \pm 1{\cdot}0°$$

From these measurements, and the assumption of a planar molecule with the axes *L* and *M* at right angles, the orientation given in Table 1 was calculated, the nine relations given in the coronene analysis [6] being used.

From the final co-ordinates given in Table 3 the structure factors and phase constants were calculated for the two principal zones (*h*0*l*) and (0*kl*). These results are given in Table 5 under $F_{calc.}$ and $\alpha°_{calc.}$ In these calculations an empirical scattering curve with the following *f* values was used :

$\sin\theta$ (λ = 1·54)	0·1	0·2	0·3	0·4	0·5	0·6	0·7	0·8	0·9
f_e (max. = 100)	90·0	74·0	56·6	39·5	24·6	16·0	10·8	7·1	4·6

These values include an appropriate mean temperature factor, although there is some evidence that better agreements might be reached if different temperature factors were used for the two zones examined. The mean discrepancies between observed and calculated structure factors, expressed in the usual way, are 14·8% for the (*h*0*l*) zone and 21% for the (0*kl*) zone.

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[*Received, October 26th*, 1955.]

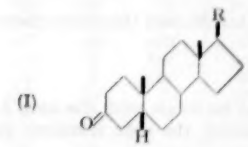
[8] J. M. Robertson, *Phil. Mag.*, 1934, **18**, 729.

196. *Long-range Effects in Alicyclic Systems. Part I. The Rates of Rearrangement of Some Steroidal Dibromides*

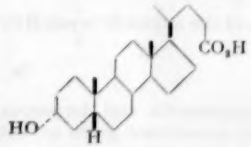
By D. H. R. Barton and A. J. Head.

The rates of mutarotation of some steroidal 5α : 6β-dibromides have been investigated. 5α : 6β : 22ξ : 23ξ-Tetrabromostigmastane reacts at only 75% of the rate observed with 5α : 6β-dibromo-cholestane and -stigmastane. The rate of rearrangement of 5α : 6β-dibromodeoxytigogenin is similar. These anomalies represent long-range effects in systems which are conformationally unambiguous.

The intramolecular interaction of functional groups through a chain of saturated carbon atoms is germane to organic chemistry. Short-range interactions through a few carbon atoms are well understood and have recently been discussed authoritatively by Ingold.[1] Longer-range interactions, involving unit polar charges, are exemplified by the classical work of Gane and Ingold [2] on the dissociation constants of aliphatic dicarboxylic acids. Some interaction, transmitted through three or four saturated carbon atoms, was found by Conant and his collaborators [3] in observations on the rate of displacement of chloride ion from alkyl chlorides by iodide ion. Much more spectacular effects have been claimed by Rothen [4] involving enzyme–substrate interactions through several hundred Å of inert material. Such claims are difficult to justify on a physical basis and have been the subject of criticism.[5] Another remarkable report was made by Marker *et al.*[6] that the point of oxidative cleavage in ring A of coprostanone (I; R = C_8H_{17}) and of pregnane-3 : 20-dione (I; R = COMe) was at $C_{(2)}$: $C_{(3)}$ whereas that of lithocholic acid (II) was at $C_{(3)}$: $C_{(4)}$.[7] Arguments recently adduced by Georg [8] show that Marker's 2 : 3-*seco*-dicarboxylic acids



(I)



(II)

are really 3 : 4-*seco*-compounds and that, in fact, no long-range effects are involved. It is well known that minor changes in steroidal side chains may inhibit digitonide formation. This is not a long-range phenomenon but a function of the crystal lattice. Catalytic-hydrogenation effects, where surface–molecule interactions are concerned, belong to the same category.

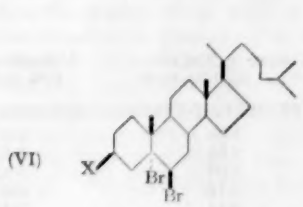
The present series of investigations was undertaken because of the paucity of knowledge of long-range effects in molecules of rigid conformation. Studies with aliphatic compounds, such as those cited above, deal with molecules of flexible conformation where the distances between functional groups in solution cannot be defined with precision. With molecules where the stereochemical nature defines the conformation quite exactly (for example, *trans*-A/B steroids and triterpenoids of the β-amyrin or lanosterol type) the possible existence of long-range effects can be explored with a precision governed only by the difficulties of practical measurement. Our first objective has been to establish the existence of long-range effects in such molecules; it is hoped to discuss their origin later.[9]

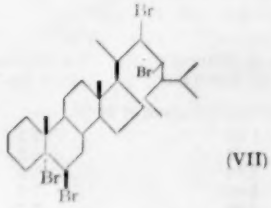
[1] Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, New York, 1953, Chap. 2.
[2] Gane and Ingold, *J.*, 1928, 1594, 2267; 1929, 1691; 1931, 2153.
[3] Conant *et al.*, *J. Amer. Chem. Soc.*, 1924, **46**, 232; 1925, **47**, 476, 488.
[4] Rothen, *Helv. Chim. Acta*, 1950, **33**, 834; *J. Amer. Chem. Soc.*, 1948, **70**, 2732; and references there cited.
[5] Trurnit, *Science*, 1950, **112**, 329; see also Rothen, *ibid.*, p. 330.
[6] Marker, Wittle, Plambeck, Rohrmann, Krueger, and Ulshafer, *J. Amer. Chem. Soc.*, 1939, **61**, 3317.
[7] Wieland, Dane, and Scholz, *Z. physiol. Chem.*, 1932, **211**, 261.
[8] Georg, *Arch. Sci.*, 1954, **7**, 114.
[9] See Barton, *Experientia*, 1955, Suppl. II, p. 121.

In general, however, we shall not be concerned with processes in which the interaction of unit polar charges is involved, and we intend to focus attention more upon conformational aspects of interaction.

The present paper is concerned with rates of rearrangement of steroidal 5α : 6β-dibromides (III) to give 5β : 6α-dibromides (IV) *via* a transition state [10] which may be symbolised [11] as in (V). Grob and Winstein [10,12] showed that this was a first-order

process, conveniently studied polarimetrically. The reaction is reversible. In cholestane derivatives (VI) the position of equilibrium varies to a first approximation with the size of the group X attached at $C_{(3)}$. Illustrative data are summarised in Table 1. For detailed





kinetic work a series of 5α : 6β-dibromides was chosen where X = H. By a study of the rearranged 5β : 6α-dibromides it was demonstrated in each case that the equilibrium was more than 99% in favour of the 5β : 6α-dibromides.

TABLE 1.

Cholestane derivative; 3β-substituent X	5β : 6α-Dibromide (%) at equilm. at 40·0°	Cholestane derivative; 3β-substituent X	5β : 6α-Dibromide (%) at equilm. at 40·0°
H	>99% *	OH	85·5 *
Cl	13	OBz	80 †
Br	10		

* Grob and Winstein.[10] † Grob and Winstein [10] report 83·7% at about 61·2°.

In agreement with Grob and Winstein [10] the rearrangement of 5α : 6β-dibromocholestane showed good first-order kinetics up to 70% or more of completion of reaction. The data obtained are summarised in Table 2 and indicate rate constants of $1{\cdot}37 \times 10^{-5}$ and of $7{\cdot}00 \times 10^{-5}$ at 25·25° and 40·03° respectively, in fair agreement with those (1·1 and $6{\cdot}4 \times 10^{-5}$ sec.$^{-1}$ respectively) reported by Grob and Winstein [10] in their less detailed examination of the kinetics of the process. In order to show that the reaction was indeed intramolecular the variation of rate constant with concentration was investigated (see Table 3). There was no significant variation in k over a nine-fold variation in concentration. The rate-constant equation for the mutarotation was found to be $k = 10^{10{\cdot}1} \exp(-20{,}400/RT)$ sec.$^{-1}$.

An analogous study was then carried out in the stigmasterol series. Stigmasterol was converted into stigmasta-5 : 22-diene which on bromination gave 5α : 6β : 22ξ : 23ξ-tetrabromostigmastane (VII) which rearranged smoothly in chloroform solution to give the 5β : 6α-coprostigmastane derivative. The kinetics of this process (Table 2) were carefully examined and shown to be of the first order and independent of concentration (see Table 3). At all temperatures the rearrangement of the 5α : 6β : 22ξ : 23ξ-tetrabromostimastane was

[10] Grob and Winstein, *Helv. Chim. Acta*, 1952, **35**, 782.
[11] See Alt and Barton, *J.*, 1954, 4284.
[12] See also Bretschneider, Földi, Galinovsky, and Fodor, *Ber.*, 1941, **74**, 1451.

significantly slower than that of 5α : 6β-dibromocholestane. The rate-constant equation was shown to be $k = 10^{10\cdot6} \exp(-20{,}400/RT)$ sec.$^{-1}$.

TABLE 2.

Temp.	Mean velocity const. 10^5k (sec.$^{-1}$)	No. of runs	Mean error (%) of mean k	Temp.	Mean velocity const. 10^5k (sec.$^{-1}$)	No. of runs	Mean error (%) of mean k
5α : 6β-*Dibromocholestane.*				5α : 6β : 22ξ : 23ξ-*Tetrabromostigmastane.*			
28·0°	1·87	6	0·5	20·0°	0·558	5	0·9
35·0	4·19	9	1·7	35·0	3·00	6	1·5
41·0	7·86	8	0·9	40·0	5·51	7	0·4
				49·0	13·4	4	0·6
5α : 6β-*Dibromostigmastane.*				5α : 6β-*Dibromodeoxytigogenin.*			
29·95	2·3	2	—	36·0	3·15	7	1·5
36·0	4·39	3	—	41·0	5·47	2	—
45·0	12·3	2	—	48·0	11·1	2	—

TABLE 3.

Concn. (g./100 ml.) of 5α : 6β-dibromide	Velocity const. 10^5k (sec.$^{-1}$)	Concn. (g./100 ml.) of 5α : 6β-dibromide	Velocity const. 10^5k (sec.$^{-1}$)
5α : 6β-*Dibromocholestane at* 41·0°.		5α : 6β : 22ξ : 23ξ-*Tetrabromostigmastane at* 40·0.	
1·06	7·7	1·08	5·3
2·02	8·2	2·91	5·55
3·79	7·8	3·07	5·45
3·89	7·7	5·16	5·6
3·96	7·75	9·71	5·55
4·03	7·75		
4·92	8·1		
9·30	7·75		
Mean	7·86		

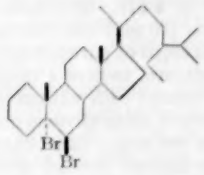
At first we were loth to accept this difference as real and an alternative explanation was sought. The difference could be due to complication of the reaction by rearrangement of the 22 : 23-dibromide grouping. This was shown not to be correct as follows. Stigmasteryl benzoate was converted into its tetrabromide which was selectively debrominated [13] to stigmasteryl benzoate 22 : 23-dibromide. The latter showed no sign of rearrangement in chloroform solution and gave back the original tetrabromide on bromination. The side-chain dibromide grouping cannot, therefore, be undergoing rearrangement during the time required for the study of the mutarotation. The difference could be explained by incomplete transformation of stigmasta-5 : 22-diene into its tetrabromide. This explanation was also rejected since several batches of tetrabromide, whose bromine content was checked by analysis, all gave the same results. Further, Dr. A. W. Burgstahler, whose kind collaboration we acknowledge, repeated the preparation of both 5α : 6β-dibromocholestane and 5α : 6β : 22ξ : 23ξ-tetrabromostigmastane and checked the kinetic data independently. The difference could also possibly be explained if the small quantity of hydrogen bromide produced in a side reaction catalysed [14] the process. We reject this, first, because of the reproducibility of our results and, secondly, because the influence of hydrogen bromide has already been shown to be negligible by Grob and Winstein.[10]

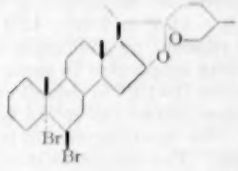
The structural difference between (VI) and (VII) consists of an extra ethyl group and two extra bromine atoms. That it is the two bromine atoms that are of importance in creating a rate-constant difference was made probable by showing that an extra ethyl group had no effect. Thus β-sitosterol was converted into stigmast-5-ene and thence into 5α : 6β-dibromostigmastane (VIII). The latter was smoothly rearranged to 5β : 6α-dibromocoprostigmastane in chloroform solution. The kinetics of this rearrangement were studied (see Table 2), although not in great detail. The reaction was of the first order

[13] Cf. Fernholz and Stavely, *J. Amer. Chem. Soc.*, 1939, **61**, 2956.
[14] Cf. Kwart and Weisfield Abs. Amer. Chem. Soc. Meeting, Cincinatti, 1955, p. 49N.

and *identical in rate* with that of 5α : 6β-dibromocholestane. The rate-constant equation was $k = 10^{10\cdot1} \exp(-20{,}400/RT)$ sec.$^{-1}$.

Finally, the effect of a more radical structural modification of the side chain was investigated. Diosgenin was converted by conventional methods into deoxydiosgenin which afforded 5α : 6β-dibromodeoxytigogenin (IX) on bromination. This was smoothly

(VIII) 

 (IX)

rearranged in chloroform solution to give 5β : 6α-dibromodeoxycoprotigogenin. The kinetics of this process were investigated (see Table 2). The reaction was of the first order but significantly slower than that of 5α : 6β-dibromocholestane. The rate-constant equation was found to be given by $k = 10^{10\cdot0} \exp(-20{,}400/RT)$ sec.$^{-1}$. The appropriate model experiments showed that the rate measurements were not being invalidated by the action of traces of hydrogen bromide on the steroidal sapogenin side chain.

In summary it may be stated that, if the rates of mutarotation of 5α : 6β-dibromocholestane and -stigmastane are represented as 100, the corresponding rates for 5α : 6β : 22ξ : 23ξ-tetrabromostigmastane and 5α : 6β-dibromodeoxytigogenin are 75 and 69 respectively. The difference in reaction rate between 5α : 6β-dibromocholestane and

TABLE 4.

Parent compound	$[M]_D$ 5α : 6β-Dibromide	5β : 6α-Dibromide	$\Delta[M]_D$
Cholest-5-ene	−215°	+267°	+482°
Stigmast-5-ene	−197	+274	+471
22ξ : 23ξ-Dibromostigmast-5-ene	−226	+246	+472
Deoxydiosgenin	−586	−158	+428

5α : 6β : 22ξ : 23ξ-tetrabromostigmastane represents a long-range effect in conformationally unambiguous systems transmitted through six saturated carbon atoms or (from accurate scale models) through 9·3 Å.

No correlation was apparent between molecular-rotation anomalies (Table 4) and reaction rates.

EXPERIMENTAL

For general experimental details see Barton *et al.*[15] All rotations refer to $CHCl_3$ solutions : the solvent was purified by washing it twice with concentrated sulphuric acid and then with aqueous sodium carbonate, dried ($CaCl_2$), and stored in the dark; it was checked for the development of acidity before use. The thermostat was controlled to within ±0·03°.

The procedure in a kinetic run was as follows. The dibromide was weighed into a calibrated 10 ml. flask which had been painted black to exclude light, except for a small window at the graduation mark, then dissolved in pure chloroform in a thermostat at the required temperature, and the solution was quickly made up to 10 ml. Samples (approx. 1 ml.), withdrawn at suitable intervals, were rapidly cooled (ice-bath) to room temperature and the rotation was determined. Concentrations of 3—4% w/v were used unless specified otherwise. Allowance was made for the difference between the temperature at which the solutions were made up and that at which the rotations were measured by using the coefficients of expansion of chloroform.[16] Values of k were calculated graphically, for greatest accuracy, on observations up to 50% reaction in the usual way.[10]

Recrystallisations of metastable dibromides were conducted at or below room temperature.

[15] Barnes, Barton, Fawcett, and Thomas, *J.*, 1952, 2339.
[16] "Handbook of Chemistry and Physics," 31st Edn., Chem. Rubber Publ. Co., Cleveland, Ohio, 1949.

These dibromides were conveniently prepared by dissolving the hydrocarbon in chloroform–acetic acid containing approx. 1·2 mols. of sodium acetate at 0° and adding 1·1 mols. of bromine in acetic acid.[17]

Derivatives of Cholestane.—**5α : 6β**-Dibromocholestane [18] had a constant $[\alpha]_D$ −40·5°. The derived **5β : 6α**-dibromocoprostane had a constant $[\alpha]_D$ +50·4° (*c*, 7·62), unchanged at room temperature overnight. **5α : 6β**-Dibromocholestanyl benzoate had a constant $[\alpha]_D$ −36·4° (*c*, 3·96); the derived **5β : 6α**-dibromide had $[\alpha]_D$ +83·1° (*c*, 4·41). **3β**-Chloro-**5α : 6β**-dibromocholestane [19] {$[\alpha]_D$ −51·5° (*c*, 5·85); 12·2 g.} in chloroform (50 ml.) was refluxed for 6 hr. ($[\alpha]_D$ −38·2°). After removal, by addition of methanol, of two crops of unrearranged dibromide, the mother-liquors were evaporated *in vacuo* at room temperature, to give a residue (3·0 g.; $[\alpha]_D$ +4°). This residue (1·61 g.) in chloroform (16 ml.) was treated with sodium iodide (6·45 g.) in "AnalaR" acetone (390 ml.) at 20° for 65 min. The product, in methylene dichloride (50 ml.), was ozonised at −78° until negative to tetranitromethane (30 min.), then shaken with water at room temperature. The methylene dichloride layer was filtered through alumina. Removal of the solvent *in vacuo* at room temperature and crystallisation at <20° from chloroform–methanol gave **5β : 6α-*dibromo*-3β-*chlorocoprostane*** (540 mg.), m. p. 126—127°, $[\alpha]_D$ +49·1° (*c*, 4·76) (Found: C, 57·75; H, 8·05; Cl + Br, 34·3. $C_{27}H_{44}ClBr_2$ requires C, 57·4; H, 8·05; Cl + Br, 34·55%). **3β : 5α : 6β**-Tribromocholestane [20] had $[\alpha]_D$ −51·5° (*c*, 3·91).

Equilibrium measurements made with these compounds at 40·0° in chloroform solution are summarised in Table 5.

TABLE 5.

Cholestane derivative; 3β-	Initial composition 5α : 6β-Dibromide	5β : 6α-Dibromide	Total concn. (g./100 ml.)	$[\alpha]_D$ Initial	Final	Time of equiln. (hr.)	5β : 6α-Dibromide (%) at equilm.
Chloride	100	0	5·51	−51·5°	−37·9°	162	13
	100	0	4·87	−50·7	−36·2	263	14
	89·9	10·1	6·09	−40·6	−37·3	144	13
	81·9	18·1	6·19	−33·0	−37·8	144	13
Bromide	100	0	4·46	−51·4	−41·9	257 *	10 †
Benzoyloxy ...	100	0	5·35	−36·4	+57·4	163	79
	0	100	5·71	+81·2	+58·6	163	80
	14·8	85·2	5·58	+62·9	+60·2	220	81
	23·7	76·3	6·15	+54·1	+60·3	213	81

* Preceded by storage for 21 days at room temperature.

† Based on $[\alpha]_D$ +41·9° for the **5β : 6α**-isomer; the latter rotation was calculated from the observed molecular-rotation difference on isomerisation of **5α : 6β**-dibromo-**3β**-chlorocholestane.

Derivatives of Stigmastane.—Stigmasterol was converted into 3β-chlorostigmasta-5 : 22-diene.[21,22] Reduction of this chloride with an equal weight of sodium in refluxing *n*-pentyl alcohol as for the preparation for cholest-5-ene gave ***stigmasta*-5 : 22-*diene***, needles (from ethyl acetate), m. p. 115—116°, $[\alpha]_D$ −69° (*c*, 2·86) (Found: C, 87·9; H, 12·3. $C_{29}H_{48}$ requires C, 87·8; H, 12·2%). Treatment with bromine (2·2 mols.) as detailed above gave **5α : 6β : 22ξ : 23ξ-*tetrabromostigmastane***, m. p. 196—198° (from chloroform–ethyl acetate–methanol), $[\alpha]_D$ −31·6° (*c*, 3·60) (Found: C, 48·7; H, 6·5; Br, 45·2. $C_{29}H_{48}Br_4$ requires C, 48·65; H, 6·8; Br, 44·6%). The m. p. recorded is that observed after drying at room temperature; if examined immediately after crystallisation a metastable (solvated) form of much lower m. p. is discernible.

Refluxing a solution of this tetrabromide in chloroform for 4 hr. gave **5β : 6α : 22ξ : 23ξ-*tetrabromocoprostigmastane***, stout needles (from ethyl acetate–methanol), m. p. 202—203° (decomp.), $[\alpha]_D$ +35·0° (*c*, 4·70), unchanged after 8 days in the dark at room temperature (Found: C, 48·7; H, 6·5; Br, 44·8%).

Stigmasterol benzoate was brominated with 2·2 mols. of bromine in the usual way, to give **5α : 6β : 22ξ : 23ξ-*tetrabromostigmastan*-3β-*yl benzoate*** (from chloroform–ethyl acetate–methanol), m. p. 148—150° (depends markedly on rate of heating), $[\alpha]_D$ −31·2° (*c*, 2·21) (Found: C, 51·9; H, 6·45; Br, 38·0. $C_{36}H_{52}O_2Br_4$ requires C, 51·7; H, 6·25; Br, 38·2%). The tetrabromide

[17] Cf. Windaus, *Ber.*, 1906, **39**, 518.
[18] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066.
[19] Marker, Whitmore, Kamm, Oakwood, and Blatterman, *ibid.*, 1936, **58**, 338.
[20] Beynon, Heilbron, and Spring, *J.*, 1936, 907, and references there cited.
[21] Windaus and Hauth, *Ber.*, 1906, **39**, 4378.
[22] Shoppee, *J.*, 1946, 1147.

was converted into the 22 : 23-dibromide as follows.[23] The tetrabromide (1·2 g.) in benzene (10 ml.) was treated with sodium iodide (800 mg.) in ethanol (7 ml.) and set aside at room temperature for 20 hr. Crystallisation of the product from benzene–ethanol afforded 22ξ : 23ξ-*dibromostigmast-5-en-3β-yl benzoate*, m. p. 182—185° (decomp.) (depends on rate of heating), $[\alpha]_D$ −6·2° (*c*, 2·73; unchanged for 5 days) (Found : C, 64·0; H, 7·75; Br, 24·0. $C_{36}H_{52}O_2Br_2$ requires C, 63·9; H, 7·75; Br, 23·6%). Treatment with 1·1 mols. of bromine in the usual way gave back the previously described 5α : 6β : 22ξ : 23ξ-tetrabromostigmastan-3β-yl benzoate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ −30° (*c*, 3·70)}.

β-Sitosterol Derivatives.—β-Sitosterol was converted into stigmast-5-ene, m. p. 76—77° (from ethyl acetate–methanol), $[\alpha]_D$ −53° (*c*, 4·20) (Found : C, 87·75; H, 12·5. Calc. for $C_{29}H_{50}$: C, 87·35; H, 12·65%), as described earlier. Treatment with bromine afforded 5α : 6β-*dibromostigmastane* (from ethyl acetate–methanol), m. p. 103—104°, $[\alpha]_D$ −35·3° (*c*, 5·27) (Found : C, 62·3; H, 9·05; Br, 28·9. $C_{29}H_{50}Br_2$ requires C, 62·35; H, 9·0; Br, 28·6%). When this dibromide was refluxed in chloroform solution for 6 hr. it gave 5β : 6α-*dibromostigmastane*, m. p. 123—125° (from ethyl acetate–methanol), $[\alpha]_D$ +49·1° (*c*, 5·54) (Found : C, 62·7; H, 8·85; Br, 28·4%).

Derivatives of Diosgenin.—Dried purified diosgenin (1·76 g.) in dry alcohol-free chloroform (50 ml.) at −60° was treated with phosphorus pentachloride (1·08 g., 1·2 mols.) with good stirring. The stirring was continued and the mixture allowed to come to room temperature (1 hr.). Crystallisation from ethyl acetate–methanol gave the chloride (55%), m. p. 204—209°, $[\alpha]_D$ −111° (*c*, 3·80). Reduction of the chloride with sodium–pentyl alcohol or, more conveniently, with sodium–propan-1-ol, afforded deoxydiosgenin (80%), m. p. 190—198° $[\alpha]_D$ −144° (*c*, 5·07).[24] The homogeneity of this material was established by extensive chromatographic fractionation. Treatment with bromine in the usual way showed (by titration) an uptake of only one mol.; crystallisation from chloroform–methanol gave 5α : 6β-*dibromodeoxytigogenin*, m. p. 167—169° (decomp.) (but rather variable), $[\alpha]_D$ −105° (*c*, 3·37) (Found : C, 58·45; H, 7·35; Br, 28·75. $C_{27}H_{42}O_2Br_2$ requires C, 58·05; H, 7·6; Br, 28·6%). Rearrangement was conveniently effected by leaving the dibromide in chloroform solution at 36° for 21 hr. Crystallisation of the product from ethyl acetate–methanol afforded the highly crystalline 5β : 6α-*dibromocoprodeoxytigogenin*, m. p. 168—172°, $[\alpha]_D$ −28·3° (*c*, 4·29; unchanged after 8 days at room temperature in the dark) (Found : C, 58·25; H, 7·65; Br, 28·5%). The constitution of this compound was confirmed as follows. Debromination by stirring with zinc dust in chloroform–acetic acid gave deoxydiosgenin, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ −143° (*c*, 3·10)}. The dibromide (43·9 mg.) in "AnalaR" acetone (20 ml.) was treated with a 0·134M-solution (20 ml.) of sodium iodide in the same solvent at 0°. After 2 hr. at this temperature no debromination had occurred, whereas the corresponding 5α : 6β-dibromide was debrominated to the extent of 90% under the same conditions.

The following experiment was carried out to show that the spiro-ketal side chain was not damaged by traces of hydrogen bromide which might possibly be formed in a side reaction during mutarotation. Diosgenin acetate (241 mg.) in chloroform–acetic acid (99 : 1; 1 ml.) containing hydrogen bromide (solution 0·0099N) was left for 21 hr. at room temperature; the rotation did not change.

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[23] Windaus and Brunken, *Z. physiol. Chem.*, 1924, **140**, 47.
[24] Fujii and Matsukawa, *J. Pharm. Soc. Japan*, 1937, **57**, 27.
[25] Marker and Turner, *J. Amer. Chem. Soc.*, 1941, **63**, 767.

197. *Some New Tropine Derivatives.*

By R. Foster and H. R. Ing.

The α-methyltropic esters of tropine and ψ-tropine, together with their methiodides and decamethylene di-iodides, have been prepared. Some new derivatives of α-ecgonine methyl ester have also been made, *viz.*, its hexa- and deca-methylene di-iodides, its benziloyl and *p*-aminobenzoyl esters, and the hexa- and deca-methylene di-iodides of α-cocaine.

(−)-Hyoscyamine salts are readily racemized in solution and consequently atropine is normally used clinically although it is only half as active as (−)-hyoscyamine in most of its pharmacological properties. It was thought that the α-methyltropic esters of tropine and ψ-tropine, the optical isomerides of which should racemize much less readily than the tropic esters, were worthy of pharmacological investigation. The esters were obtained by transesterification of tropine and ψ-tropine with ethyl α-methyltropate; the corresponding methiodides and decamethylene di-iodides were also prepared. The pharmacology of these compounds will be reported elsewhere but preliminary results indicate that both esters and their methiodides possess atropine-like properties, but are less potent than atropine.

α-Methyltropic acid was prepared by the following series of reactions:

$$PhCH_2{\cdot}CN + Et_2CO_3 \xrightarrow{Na} PhCH(CN){\cdot}CO_2Et \xrightarrow{Na + MeI} PhCMe(CN){\cdot}CO_2Et$$
$$\xrightarrow{H_2\text{-}Ni} PhCMe(CH_2{\cdot}NH_2){\cdot}CO_2Et \xrightarrow{HNO_2} PhCMe(CH_2{\cdot}OH){\cdot}CO_2Et \xrightarrow{Ba(OH)_2} PhCMe(CH_2{\cdot}OH){\cdot}CO_2H.$$

All stages except the final hydrolysis gave good yields; in the fourth stage the hydrochloride of the amino-ester gave a poor yield (25%), but the neutral sulphate a 65% yield, with sodium nitrite.

Willstätter [1] stated that α-cocaine, which he synthesized from tropinone cyanohydrin, lacked local-anæsthetic properties. This claim, which rested solely upon the absence of a numbing effect when α-cocaine was applied to the tongue, has remained unchallenged for nearly 60 years. We have repeated Willstätter's synthesis and, in collaboration with Dr. Varagić, have shown that α-cocaine is a potent local anæsthetic when injected, but not when applied locally to the eye.[2] We have also prepared the benzilic and *p*-aminobenzoic esters of α-ecgonine methyl ester and the hexa- and deca-methylene di-iodides of α-cocaine and α-ecgonine methyl ester.

Willstätter [1] prepared α-ecgonine methyl ester by esterifying α-ecgonine; better yields are obtained by methanolysis of tropinone cyanohydrin. α-Ecgonine should exist in two stereoisomeric forms corresponding to tropine and ψ-tropine, but conventional methods, including paper chromatography, failed to reveal a second isomer in the product obtained by methanolysis of tropinone cyanohydrin.

Experimental

α-Methyltropic Acid.—Ethyl α-cyano-α-phenylacetate was prepared from benzyl cyanide and diethyl carbonate by the method described by Hessler;[3] the ester (yield, 55%) had b. p. 157°/14 mm. (Hessler reports b. p. 165°/20 mm.). Methylation of its sodio-derivative gave ethyl α-cyano-α-phenylpropionate (yield, 92%), b. p. 140°/10 mm. (Wideqvist [4] gives 133·5°/8 mm.). This ester (100 g.) in ethanol (800 ml.) was hydrogenated in presence of Raney nickel (20 g.) at 60°/75 atm. for 6 hr. After removal of the catalyst and solvent the residue was extracted with 2N-hydrochloric acid, and the acid solution washed with ether and then basified (K_2CO_3); the amino-ester was extracted with ether, dried (K_2CO_3), and fractionated. *Ethyl β-amino-α-methyl-α-phenylpropionate* (yield 70%) had b. p. 128°/3·5 mm., n_D^{20} 1·5123 (Found: C, 69·8; H, 8·3; N, 6·8. $C_{12}H_{17}O_2N$ requires C, 69·6; H, 8·2; N, 6·8%). The

[1] Willstätter, *Ber.*, 1896, **29**, 2216.
[2] Foster, Ing, and Varagić, *Brit. J. Pharmacol.*, 1955, **10**, 436.
[3] Hessler, *Amer. Chem. J.*, 1904, **32**, 120.
[4] Wideqvist, *Svensk kem. Tidskr.*, 1943, **55**, 125.

amino-ester (50 g.) was dissolved in one equivalent of N-sulphuric acid, and one equivalent of sodium nitrite was added dropwise to the stirred solution at 0°. After 4 hr. the solution was extracted four times with ether, and the extract dried (Na_2SO_4) and evaporated. Fractionation of the residue gave *ethyl α-methyltropate* (yield, 65%), b. p. 110°/2 mm., n_D^{20} 1·4988 (Found: C, 68·9; H, 7·6. $C_{12}H_{14}O_3$ requires C, 69·2; H, 7·6%). A mixture of the ester (12 g.), barium hydroxide octahydrate (80 g.), and water (250 ml.) was boiled under reflux for 6 hr.; the solution was then acidified and extracted three times with chloroform; the extract was dried (Na_2SO_4) and evaporated; the residual oil solidified when scratched, and was recrystallized three times from benzene. *α-Methyltropic acid* forms feathery crystals (yield, 30%; m. p. 98°) easily soluble in cold water (Found: C, 66·7; H, 6·7. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%).

Tropine and ψ-Tropine α-Methyltropates.—Tropine or ψ-tropine (6—8 g.) in xylene (60 ml.) was treated with a solution of sodium methoxide [from sodium (0·12 g.) and methanol (10 ml.)]. The methanol was evaporated on the steam-bath, and ethyl α-methyltropate (10 g.) added. After removal of the xylene under reduced pressure at 90° the residue was heated at 130°/10 mm. for 4 hr. The product was dissolved in chloroform and extracted with N-hydrochloric acid. The free base was liberated by adding excess of potassium carbonate and extraction with chloroform; evaporation of the dried extract gave the free ester as a solid in 70—75% yield. The properties and analyses of the two esters and of their derivatives are given in the Table.

				Found, %			Reqd., %		
Ester	M. p.	Solvent	Formula	C	H	N	C	H	N
Tropine α-methyltropate [a]	84°	Petrol (60—80°)	$C_{13}H_{23}O_3N$	71·0	8·1	4·9	71·2	8·2	4·6
,, *perchlorate*	106—107	Dioxan	$C_{13}H_{23}O_3N,HClO_4$	53·6	6·6	—	53·6	6·4	—
,, *methiodide*	234	Ethanol	$C_{14}H_{26}O_3NI$	51·2	6·2	3·0	51·3	6·3	3·1
,, *decamethylene di-iodide* [b]	230	Ethanol	$C_{46}H_{70}O_6N_2I_2,H_2O$	54·2	7·1	2·7	54·2	7·1	2·7
,, *decamethylene di-bromide* [c]	220	Petrol (60—80°) Ether–alcohol (7 : 3 v/v)	$C_{46}H_{70}O_6N_2Br_2$	60·6	7·8	3·1	60·9	7·7	3·1
ψ-Tropine α-methyltropate [a]	86·5	Petrol (80—100°)	$C_{13}H_{23}O_3N$	71·3	8·2	4·7	71·2	8·2	4·6
,, *hydrochloride*	213	Propanol	$C_{13}H_{23}O_3N,HCl$	63·7	7·6	4·2	63·6	7·7	4·1
,, *methiodide*	196	Ethanol	$C_{14}H_{26}O_3NI$	50·9	6·1	3·1	51·3	6·3	3·1
,, *decamethylene di-iodide* [b]	231	Ethanol	$C_{46}H_{70}O_6N_2I_2,H_2O$	54·0	7·0	2·9	54·2	7·1	2·7

(*a*) A mixture of the α-methyltropates of tropine and ψ-tropine had m. p. 58—65°.
(*b*) A mixture of the decamethylene di-iodides of tropine and ψ-tropine α-methyltropates had m. p. 220°.
(*c*) Found: Br, 17·6. Requires Br, 17·7%.

α-Ecgonine Derivatives.—Crude tropinone cyanohydrin [5] (100 g.) was washed with methanol (3 × 200 ml.) and covered with anhydrous methanol (1800 ml.). The suspension was stirred, cooled to 0°, and saturated with hydrogen chloride below 4°; after being left at room temperature for 5 days, the solution was boiled under reflux for 1 hr. while a rapid stream of hydrogen chloride was passed through it. The solvent was evaporated, water (200 ml.) and excess of potassium carbonate added, and the product extracted with chloroform. α-Ecgonine methyl ester, crystallized from light petroleum (b. p. 80—100°), had m. p. 114° (Willstätter [1] records m. p. 114°); the yield was 65% on tropinone. The following derivatives were made: *Hexamethylene di-iodide salt*, crystallized from methanol–ethanol (3 : 7 by vol.), m. p. 244° (Found: C, 42·0; H, 6·2; N, 4·0. $C_{26}H_{44}O_6N_2I_2$ requires C, 42·3; H, 6·2; N, 3·8%). *Decamethylene di-iodide salt*, crystallized from ethanol, m. p. 229° (Found: C, 45·5; H, 6·7; N, 3·5. $C_{30}H_{54}O_6N_2I_2$ requires C, 45·5; H, 6·7; N, 3·5%). α-Cocaine, prepared by Willstätter's method; [1] hydrochloride, crystallized from pentyl acetate, m. p. 180° (Found: C, 60·0; H, 6·6; N, 4·1. Calc. for $C_{17}H_{22}O_4NCl$: C, 60·1; H, 6·5; N, 4·1%). *Hexamethylenebis-α-cocainium di-iodide*, crystallized thrice from 90% methanol, m. p. 244° (decomp.) (Found: C, 50·6; H, 5·9; N, 2·8. $C_{40}H_{54}O_8N_2I_2$ requires C, 50·9; H, 5·7; N, 3·0%). *Decamethylenebis-α-cocainium di-iodide*, crystallized twice from ethanol, m. p. 182—185° (Found: C, 52·6; H, 6·3; N, 2·9. $C_{44}H_{62}O_8N_2I_2$ requires C, 52·8; H, 6·2; N, 2·8%). *Benzilyl-α-ecgonine methyl ester* was made by heating α-ecgonine methyl ester (10 g.) with α-chlorodiphenylacetyl chloride (14 g.) in dry

[5] Willstätter, *Ber.*, 1896, **29**, 1575.

benzene (100 ml.) for 8 hr. Water (100 ml.) and excess of potassium carbonate were added to the cooled product, and the mixture was left overnight in order to effect hydrolysis of the α-chloro-group. The benzilic ester was extracted with chloroform (3 × 50 ml.), the solvents were evaporated, and the residual solid was crystallized from 70% ethanol; the ester (yield 20%) had m. p. 130° (Found : C, 70·2; H, 6·5; N, 3·2. $C_{24}H_{27}O_5N$ requires C, 70·4; H, 6·6; N, 3·4%). The *methiodide*, crystallized from *iso*propyl alcohol, had m. p. 196° (decomp.) (Found: C, 54·2; H, 5·7; N, 2·2. $C_{24}H_{27}O_5N,CH_3I$ requires C, 54·4; H, 5·4; N, 2·5%). p-*Nitrobenzoyl-α-ecgonine methyl ester*, obtained by heating α-ecgonine methyl ester (5 g.) and *p*-nitrobenzoyl chloride (10 g.) at 100° for 2 hr. and then with benzene (50 ml.) for 2 hr., crystallized from ethyl acetate or benzene (yield, 66%) had m. p. 138° (Found : C, 58·3; H, 5·9; N, 8·2. $C_{17}H_{20}O_6N_2$ requires C, 58·6; H, 5·7; N, 8·0%). Catalytic reduction of the nitrobenzoate (4·2 g.) in ethanol over Raney nickel at 3 atm. gave p-*aminobenzoyl-α-ecgonine methyl ester*, which after crystallization from ethanol had m. p. 158·5° (yield, 92%) (Found : C, 64·1; H, 6·9; N, 8·7. $C_{17}H_{22}O_4N_2$ requires C, 63·8; H, 7·0; N, 8·8%).

Department of Pharmacology, Oxford. [*Received, November 10th*, 1955.]

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198. *Studies in Peroxidase Action. Part X.* The Oxidation of Phenols.*

By H. Booth and B. C. Saunders.

The oxidation of certain phenols by hydrogen peroxide in the presence of peroxidase has been studied. Mesitol gave 4-hydroxy-3 : 5-dimethylbenzyl alcohol, 4-hydroxy-3 : 5-dimethylbenzaldehyde, and 2 : 6-dimethylbenzoquinone. The reaction involved the stepwise oxidation of the methyl group *para* to the hydroxyl group, since the alcohol (probably the primary oxidation product) was rapidly oxidised by the enzyme system to the aldehyde. The latter was converted, not into the carboxylic acid but into the quinone. Durenol was oxidised mainly to 4 : 4′-dihydroxy-2 : 3 : 5 : 6 : 2′ : 3′ : 5′ : 6′-octamethyldiphenyl. A trace of duroquinone was also isolated.

The much-used guaiacol reaction has been re-examined. Guaiacol was rapidly oxidised to a brown-red solid from which 2 : 2′-dihydroxy-3 : 3′-dimethoxydiphenyl has been isolated. Reductive acetylation of the crude product gave 4 : 4′-diacetoxy-3 : 3′-dimethoxydiphenyl in small yield.

In Parts I—IX, the detailed investigation was recorded of the action of the enzyme peroxidase on various aromatic amines in the presence of hydrogen peroxide. This work has now been extended to include phenols as substrates.

Although it has been known since 1900 that phenols are readily oxidised by the peroxidase system, most investigators have been content to record the colour changes observed; the nature of the products has rarely been examined.[1] In a few cases, however, the oxidation products have been fully characterised. Vanillin yields " dehydrodivanillin "[2] and pyrogallol gives purpurogallin.[3] Catechol is oxidised by the peroxidase system to *o*-benzoquinone, since a mixture of catechol and aniline yields 4 : 5-dianilino-*o*-benzoquinone on oxidation.[4] *p*-Cresol is converted by the enzyme into 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl, the analogous terphenyl, and a furan derivative.[5]

We have already shown that oxidation of aniline and of *p*-toluidine by the peroxidase system yields a variety of products because of the free positions in the ring where oxidation

* Part IX, *J.*, 1954, 4630.

[1] Bach and Chodat, (*a*) *Ber.*, 1903, **36**, 600; (*b*) *Arch. Sci. phys. nat.*, 1916, **42**, 56; (*c*) Chodat, *Arch. Génève*, 1907, **24**, 2; Onslow, *Biochem. J.*, 1923, **17**, 2; Szent-Györgyi, *ibid.*, 1928, **22**, 1387; Elliot, *ibid.*, 1932, **26**, 1281; Balls and Hale, *J. Biol. Chem.*, 1934, **107**, 767.

[2] Bourquelot and Marchadier, *Compt. rend.*, 1904, **138**, 1432; Lerat, *Compt. rend. Soc. Biol.*, 1903, **55**, 1325.

[3] Willstätter and Heiss, *Annalen*, 1923, **433**, 17.

[4] Pugh and Raper, *Biochem. J.*, 1927, **21**, 1370.

[5] Westerfield and Lowe, *J. Biol. Chem.*, 1942, **145**, 403.

and condensation can take place.[6] On the other hand, the oxidation of mesidine gave only one compound, *viz.*, 3 : 5-dimethyl-*p*-benzoquinone 1-(2 : 4 : 6-trimethylanil).[7] We thought it likely that similar considerations might apply to the oxidation of subsituted phenols, and therefore investigated the oxidation of mesitol and durenol. There is no reference in the literature to the enzymic oxidation of either phenol, but the oxidation of mesitol by non-enzyme systems is recorded. Using neutralised Caro's acid, Bamberger [8] claimed to have isolated 4-hydroxy-3 : 5-dimethylbenzyl alcohol (I) and 4-hydroxy-2 : 4 : 6-trimethyl-*cyclo*hexa-2 : 5-dienone, but Cosgrove and Waters [9] could not repeat his observations. Ferrous sulphate and hydrogen peroxide oxidise mesitol to a diphenylmethane derivative [10] whereas benzoyl peroxide gives 3 : 5 : 3′ : 5′-tetramethylstilbene-4 : 4′-quinone and 4-benzoyloxy-2 : 4 : 6-trimethyl*cyclo*hexa-2 : 5-dienone.[9] The stilbenequinone is also produced by the action of silver oxide.[11] Fichter and Muller [12] isolated 2 : 6-dimethyl-*p*-benzoquinone and 2-hydroxy-3 : 5-dimethylbenzoic acid by electrochemical oxidation of mesitol. Mesitol has been oxidised by lead tetra-acetate to 2-acetoxy-2 : 4 : 6-trimethyl-*cyclo*hexa-3 : 5-dienone.[13]

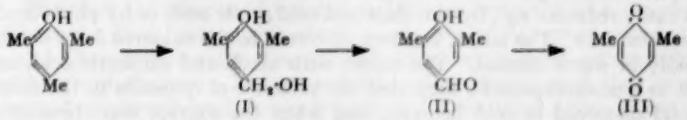
For our reactions, a highly purified specimen of peroxidase was used. An aqueous solution of mesitol, with hydrogen peroxide and peroxidase added intermittently, became yellow and later turbid; later a pale yellow solid separated. The yellow filtrate contained chiefly 4-hydroxy-3 : 5-dimethylbenzaldehyde (II) and 2 : 6-dimethylbenzoquinone (III).

Smith, Opie, Wawzonek, and Prichard [14] prepared this quinone from 3 : 5-xylenol in 74% yield. By their method we obtained a yield of only 65%, and the product was contaminated with a phenol difficult to remove except by selective adsorption on alumina. We found it easier to prepare the pure quinone (required for comparison) by allowing 3 : 5-dimethyl-4-nitrosophenol to react with cuprous oxide and hydrochloric acid in 2-ethoxyethanol.[15]

An authentic sample of 4-hydroxy-3 : 5-dimethylbenzaldehyde was prepared in poor yield by a Reimer–Tiemann reaction and in 50% yield by modification [16] of the Gattermann reaction.

The yellow amorphous solid precipitated during the peroxidase oxidation of mesitol was fractionally sublimed in a high vacuum and gave impure 4-hydroxy-3 : 5-dimethylbenzyl alcohol (I), m. p. 93·5—95·5°. The pure alcohol had m. p. 103·5—105°; the low m. p. of the enzymic product was due to traces of the corresponding aldehyde, since the infrared absorption curve showed a peak where absorption due to this type of carbonyl group normally occurs.

An aqueous solution of the alcohol was very rapidly oxidised to the corresponding aldehyde by the enzyme system. We also noted that 4-hydroxy-3 : 5-dimethylbenzaldehyde was attacked by the system, giving 2 : 6-dimethyl-*p*-benzoquinone. Thus we have

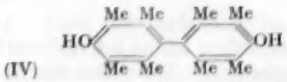


evidence for the enzymic oxidation of mesitol according to the annexed scheme (in particular it should be noted that the carboxylic acid is not formed). Qualitative experiments showed that the quinone was unaffected by the enzyme system and was thus a true end-product of the oxidation.

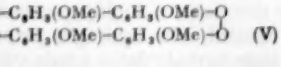
[6] P. J. G. Mann and Saunders, *Proc. Roy. Soc.*, 1935, *B*, **119**, 47; Saunders and P. J. G. Mann, *J.*, 1940, 769.
[7] Chapman and Saunders, *J.*, 1941, 496.
[8] Bamberger, *Ber.*, 1903, **36**, 2030.
[9] Cosgrove and Waters, *J.*, 1951, 388.
[10] *Idem*, *J.*, 1951, 1726.
[11] Goldschmidt and Bernard, *Ber.*, 1923, **56**, 1963.
[12] Fichter and Muller, *Helv. Chim. Acta*, 1935, **18**, 831.
[13] Wessely, Lauterbach-Keil, and Sinwell, *Monatsh.*, 1950, **81**, 1055.
[14] Smith, Opie, Wawzonek, and Prichard, *J. Org. Chem.*, 1939, **4**, 318.
[15] Cf. Sumerford and Dalton, *J. Amer. Chem. Soc.*, 1944, **66**, 1330.
[16] Adams and Levine, *J. Amer. Chem. Soc.*, 1923, **45**, 2373.

Further, mesitol and the intermediate compounds in the oxidation were scarcely attacked by hydrogen peroxide or peroxidase alone. In most of these control experiments, the starting material was recovered in high yield. However, when 4-hydroxy-3 : 5-dimethylbenzaldehyde was treated with hydrogen peroxide alone, a faint yellow colour appeared in the solution after several days. No solid separated and 64—70% of the aldehyde was recovered. It was concluded that hydrogen peroxide alone oxidises the aldehyde so slowly that this reaction may be neglected when the enzyme system is present. Thus all the oxidations described were brought about by peroxidase action.

There is no mention in the literature of the oxidation of durenol, by either inorganic reagents or enzyme systems. Durenol is very slightly soluble in cold water and it was therefore oxidised in fine suspension. Hydrogen peroxide and peroxidase were added intermittently during 5 days. No colour changes were observed and a white precipitate was always present in suspension. The precipitate consisted of unchanged durenol and 4 : 4′-dihydroxyoctamethyldiphenyl (IV). The filtrate yielded traces of crude duroquinone.



(IV)



(V)

Many workers, *e.g.*, Bach and Chodat,[16] have noted that guaiacol is oxidised by the peroxidase system to a red substance. Ucko and Bansi [17] gave the optimum pH for the reaction as 5—5·2; Chance,[18] however, found that the velocity of reaction of his " complex II " with guaiacol was little affected by pH in the range 3·4—5·3. Bertrand [19] oxidised guaiacol with the enzyme laccase and obtained a red " tetraguaiacoquinone," which he formulated as the peroxide (V). This formula is, of course, improbable because it does not account for the red colour of the compound. Mann [20] used the reaction of peroxidase with guaiacol to investigate the kinetics of peroxidase action.

The action of inorganic oxidising agents on guaiacol has received little attention. Kar [21] reported the oxidation of guaiacol to " tetraguaiacoquinone " by hydrogen peroxide and catalytic amounts of tungstic, molybdic, and vanadic acid sols. Pennington and Ritter [22] showed that one molecule of guaiacol absorbed 3 molecules of periodate, a red colour being produced. By electrochemical oxidation of guaiacol, in sulphuric acid, using a lead anode, Fichter and Dietrich [23] isolated 4 : 4′-dihydroxy-3 : 3′-dimethoxydiphenyl. Potassium nitrosodisulphonate gives methoxy-*p*-benzoquinone.[24]

When a solution of guaiacol in acetate buffer (pH 5·0) was treated with hydrogen peroxide and peroxidase, the product was a brown solid with a green metallic lustre, m. p. 110—160°, soluble in sodium hydroxide and sodium carbonate solutions. With concentrated sulphuric acid it gave a transient green colour and finally a brown solution. The brown solid was easily reduced, *e.g.*, by zinc dust and cold acetic acid, or by phenylhydrazine, to a colourless substance The latter, however, reverted to the coloured form slowly in air and very rapidly in warm alcohol. The colour with alkali and sulphuric acid, and the easy reduction to leuco-compounds, suggested the presence of quinones in the mixture. Most of the solid dissolved in cold benzene, and when the extract was chromatographed on neutral alumina several coloured zones were observed. However, no crystals were obtained by elution from the column.

When the crude mixture was sublimed in a high vacuum, a small quantity of white solid was isolated, which crystallised from *cyclo*hexane in colourless plates, m. p. 141°. Analysis and molecular-weight determinations gave $C_{14}H_{14}O_4$, suggesting a dehydrodiguaiacol. The product was phenolic, and gave a blue colour with 2 : 6-dichloroquinone

[17] Ucko and Bansi, *Z. physiol. Chem.*, 1926, **159**, 235.
[18] Chance, *Arch. Biochem.*, 1949, **24**, 410.
[19] Bertrand, *Bull. Soc. chim. France*, 1904, **31**, 185; *Compt. rend.*, 1903, **137**, 1270; *Ann. Inst. Pasteur*, 1904, **18**, 116.
[20] Mann, *Biochem. J.*, 1931, **25**, 918.
[21] Kar, *J. Indian Chem. Soc.*, 1937, **14**, 291.
[22] Pennington and Ritter, *J. Amer. Chem. Soc.*, 1947, **69**, 187.
[23] Fichter and Dietrich, *Helv. Chim. Acta*, 1924, **7**, 137.
[24] Teuber and Jellinck, *Chem. Ber.*, 1952, **85**, 95.

chloroimide, showing that at least one of the two aromatic rings had an unsubstituted position *para* to a hydroxyl group. The compound evidently had structure (VI) or (VII).

When 2 : 2′-dihydroxy-3 : 3′-dimethoxydiphenyl (VI) was synthesised (see below) it crystallised from *cyclo*hexane in needles, m. p. 142·5—143°, and mixed m. p. with enzymic product 141°. Both compounds gave an orange-red colour with ferric chloride in aqueous alcohol and an orange-red colour with peroxidase and hydrogen peroxide. The infrared absorption spectra were identical. It was concluded that the enzymic product was essentially 2 : 2′-dihydroxy-3 : 3′-dimethoxydiphenyl.

This product (VI) was synthesised from vanillin. With ferric chloride this gave dehydrodivanillin and acetylation gave 2 : 2′-diacetoxy-5 : 5′-diformyl-3 : 3′-dimethoxydiphenyl. Potassium permanganate oxidised the latter to 2 : 2′-diacetoxy-3 : 3′-dimethoxydiphenyl-5 : 5′-dicarboxylic acid, m. p. 277—280° (Elbs and Lerch[25] recorded 140°). The acetyl groups were next removed and the hydroxy-acid was decarboxylated to 2 : 2′-dihydroxy-3 : 3′-dimethoxydiphenyl (VI).

An unsuccessful attempt was made to synthesise the compound (VI) by an Ullmann reaction. 6-Nitroguaiacol was converted into toluene-*p*-sulphonate and then reduced to the amine. Diazotisation and treatment with hydriodic acid gave a poor yield of the toluene-*p*-sulphonate of 6-iodoguaiacol. Preparation of 6-iodoguaiacol from the diazonium salt of 6-aminoguaiacol was unsuccessful owing to the formation of 7-methoxybenz-1 : 2 : 3-oxadiazole, orange crystals, which exploded at 110° and coupled with alkaline β-naphthol to give a red dye.

When the iodoguaiacol toluene-*p*-suphonate was heated with activated copper bronze at 250°, an intractable solid resulted, but a small quantity of the required 3 : 3′-dimethoxy-2 : 2′-di-*p*-toluenesulphonyloxydiphenyl was isolated. Attempts to hydrolyse the ester by two methods were unsuccessful, probably owing to steric hindrance; in this connection it is interesting that heating 2 : 2′-dihydroxy-3 : 3′-dimethoxydiphenyl with toluene-*p*-sulphonyl chloride in hot pyridine for an hour (conditions normally giving good yields) gave only a small yield of the ester.

When the crude oxidation product from guaiacol was heated with acetic anhydride, zinc dust, and sodium acetate, white amorphous solid was obtained. Fractional crystallisation was ineffective, but fractional sublimation gave colourless crystals, m. p. 195·5—197·5°. Analyses indicated that this was probably the diacetate of a dehydrodiguaiacol. The diacetate of 2 : 2′-dihydroxy-3 : 3′-dimethoxydiphenyl was synthesised and had m. p. 133—134°. Therefore the compound isolated was almost certainly 4 : 4′-diacetoxy-3 : 3′-dimethoxydiphenyl. In support of this, the m. p. of our product agrees with that recorded by Fichter and Dietrich[23] for the diacetate of dehydrodiguaiacol obtained by electrochemical oxidation of guaiacol. Fichter and Dietrich suggested that their product was 4 : 4′-dihydroxy-3 : 3′-dimethoxydiphenyl because it did not react with nitrous acid (thus positions *para* to the hydroxyl group were substituted), and with hydriodic acid it gave a tetrahydroxydiphenyl different from the 2 : 3 : 2′ : 3′-tetrahydroxydiphenyl.[26] The isolation of 4 : 4′-diacetoxy-3 : 3′-dimethoxydiphenyl by reductive acetylation of the crude oxidation product shows that the latter contains 3 : 3′-dimethoxydipheno-4 : 4′-quinone. The characteristic red-brown of the crude guaiacol oxidation product is undoubtedly due partly to this quinone. The crude product also probably contains the isomeric 3 : 3′-dimethoxydipheno-2 : 2′-quinone produced by the further oxidation of the dihydroxydiphenyl (VI), but it has not been isolated.

The fact that the oxidation of durenol gives a colourless product is undoubtedly due to the steric effects of the four *o*-methyl groups (cf. IV). Further oxidation of the diphenol (IV) to a coloured diphenoquinone would require the production of a double bond between

[25] Elbs and Lerch, *J. prakt. Chem.*, 1916, **93**, 2.
[26] Barth and Schreder, *Ber.*, 1878, **11**, 1336.

the two rings and this necessitates a shortening of the link. A model indicates that such a shortening, with retention of a planar structure, is not very likely.

Experimental

Peroxidase Solution.—The enzyme used in most experiments was a concentrated solution kindly supplied by Professor Keilin and Dr. Hartree. It was purified by the method of Keilin and Mann.[27] The solution contained 19·4 enzyme units/ml. The preparation did not oxidise catechol in the absence of hydrogen peroxide : therefore tyrosinase and laccase were absent. In oxidation experiments, solutions containing 0·3 or 0·6 enzyme unit/ml. were employed.

Oxidation of Mesitol.—Mesitol[28] (2 g.) was dissolved in distilled water (4 l.); the pH was 6·5. Peroxidase solution (10 c.c.; 0·6 unit/c.c.) was added, followed by 20-vol. hydrogen peroxide (2 c.c.). A pale yellow colour developed, followed by turbidity. The solution was stirred continuously and further quantities of enzyme (26 c.c. in all) and hydrogen peroxide (30 c.c. in all) were added at intervals during 24 hr. During oxidation the pH gradually fell to *ca.* 4·5. After addition of enzyme and hydrogen peroxide, the solution was stirred for 24 hr. and set aside for 48 hr., pale yellow solid separating. The mixture was filtered and the precipitate and filtrate were examined.

Treatment of filtrate. This was extracted six times with ether. The yellow extracts were dried (Na_2SO_4) and the ether distilled off, leaving an orange oil which was steam-distilled.

The non-volatile fraction was extracted with ether and dried (Na_2SO_4). Evaporation left a dark red solid which was digested with hot water, and the solution was filtered hot from dark intractable residue. The filtrate, on cooling, deposited white needles of 4-hydroxy-3 : 5-dimethylbenzaldehyde which, recrystallised from aqueous alcohol, had m. p. and mixed m. p. 114·5—115° [Found : C, 71·9; H, 6·8%; *M* (Rast), 130—160. Calc. for $C_9H_{10}O_2$: C, 71·9; H, 6·7%; *M*, 150]. The 2 : 4-*dinitrophenylhydrazone*, recrystallised from ethanol, m. p. 276—277° (decomp.) (Found : C, 54·4; H, 4·3; N, 17·1. $C_{15}H_{14}O_5N_4$ requires C, 54·5; H, 4·3; N, 17·0%).

The yellow steam-distillate containing orange needles was extracted with ether. Evaporation of the dried extracts gave an orange solid (0·45 g.) which was digested with light petroleum (b. p. 40—60°) at −5° until white and then crystallised from aqueous alcohol as needles (40 mg.) of 4-hydroxy-3 : 5-dimethylbenzaldehyde, m. p. 112—113·5°, mixed m. p. 113—114°. The petroleum extract gave on evaporation a yellow solid (0·4 g.) which crystallised from light petroleum (b. p. 40—60°) as pale yellow needles of pure 2 : 6-dimethyl-*p*-benzoquinone, m. p. and mixed m. p. 71·5—72° (Found : C, 70·4; H, 5·6. Calc. for $C_8H_8O_2$: C, 70·55; H, 5·9%). The quinone (70 mg.) was reductively acetylated by heating it under reflux with zinc dust (0·2 g.), acetic anhydride (10 c.c.), acetic acid (2 c.c.), and pyridine (0·2 c.c.) for 30 min.; the mixture was filtered hot and poured into water (50 c.c.); on stirring, a white solid separated and crystallised as needles, m. p. 92—93°, from aqueous alcohol (lit.,[29] m. p. 91—92°).

Treatment of precipitate. The precipitate (1 g.) was dissolved in acetone (50 c.c.), and the solution filtered, concentrated, and transferred to a sublimation tube. The acetone was removed under a moderate vacuum. Sublimation of the resulting solid at 130—140°/10^{-4} mm. gave, successively, the most volatile fraction, white crystals, m. p. 70—90°, a yellow oil, and a residual solid.

The crystals were contaminated with oil and were resublimed at 10^{-4} mm. At 60—80°, the sublimate consisted of white crystals, which were recovered by dissolving them in ether and evaporating the solution [yield 38 mg.; m. p. 94° (softened at 75°)]. Recrystallisation from carbon tetrachloride gave square prisms (11 mg.), m. p. 93·5—95·5° (Found : C, 70·2; H, 7·8. Calc. for $C_9H_{12}O_2$: C, 71·0; H, 7·95%). The mixed m. p. with pure 4-hydroxy-3 : 5-dimethylbenzyl alcohol (m. p. 103·5—104°) was 96—101°. The infrared absorption spectrum was almost identical with that of an authentic specimen of this alcohol.

The residual solid was resublimed at 5×10^{-4} mm. up to 225°, giving successively white crystals of m. p. 75—85°, white crystals of m. p. 85—105°, and yellow oil (140 mg.). The first two fractions were minute and not further examined. The yellow oil solidified to a glass, insoluble in 10% aqueous sodium hydroxide; it gave a precipitate with 2 : 4-dinitrophenylhydrazine; attempts to crystallise it were unsuccessful (Found : C, 77·0; H, 7·5%).

4-*Hydroxy*-3 : 5-*dimethylbenzaldehyde.*—2 : 6-Xylenol (20 g.) was dissolved in dry "AnalaR" benzene (70 c.c.). Zinc cyanide (37 g.) was added, the mixture cooled, and dry hydrogen

[27] Keilin and Mann, *Proc. Roy. Soc.*, 1937, *B*, **122**, 119.
[28] Porter and Thurber, *J. Amer. Chem. Soc.*, 1921, **43**, 1194.
[29] Stern, Robeson, Weisler, and Baxter, *J. Amer. Chem. Soc.*, 1947, **69**, 869.

chloride passed in for 50 min., with stirring. The flask was cooled to 0°, powdered anhydrous aluminium chloride (30 g.) added, and hydrogen chloride again passed in at 50—55° for 4 hr. After cooling, the benzene was decanted from the sticky aldimine hydrochloride. 10% Hydrochloric acid (600 c.c.) was added and the aldehyde liberated by heating the mixture under reflux for an hour. The mixture was steam-distilled to remove benzene and unchanged 2 : 6-xylenol, and then extracted with ether. The extract was shaken with saturated sodium hydrogen sulphite solution; acidification of the sulphite extracts with hot dilute sulphuric acid gave the pure aldehyde (11·5 g., 50% based on unrecovered phenol) which crystallised from aqueous alcohol in needles, m. p. 114—115°.

2 : 6-*Dimethylbenzoquinone*.—3 : 5-Dimethyl-4-nitrosophenol [30] (9 g.) was dissolved in "Methylcellosolve" (90 c.c.) and acetone (10 c.c.). Cuprous oxide (8·4 g.), concentrated hydrochloric acid (28·6 c.c.), and water (36 c.c.) were added and the mixture was heated under reflux for 75 min. The quinone was steam-distilled and extracted from the distillate with ether, which was dried (Na_2SO_4) and evaporated, to give the crude quinone (6·67 g., 88%). Crystallisation from light petroleum (b. p. 40—60°) gave yellow needles, m. p. 71·5—72°.

Peroxidase-catalysed Oxidation of 4-Hydroxy-3 : 5-dimethylbenzaldehyde.—4-Hydroxy-3 : 5-dimethylbenzaldehyde (2 g.) was dissolved in distilled water (5 l., pH 6·0). Peroxidase (10 c.c.; 0·6 unit/c.c.) and 20-vol. hydrogen peroxide (2 c.c.) were added, a yellow colour being produced. The solution was stirred for 36 hr. and enzyme (14 c.c.) and hydrogen peroxide (48 c.c.) were added in small portions at intervals. A pale yellow precipitate separated and after a further 60 hr., the solid (0·53 g.) was filtered off. The filtrate was extracted four times with ether and dried (Na_2SO_4). Evaporation yielded a yellow oil which was steam-distilled, giving pale yellow needles of 2 : 6-dimethylbenzoquinone (0·6 g.), m. p. 69—70°, a mixed m. p. being 70—71°.

Peroxidase-catalysed Oxidation of 4-Hydroxy-3 : 5-dimethylbenzyl Alcohol.—The alcohol [8] (0·49 g.) in water (150 c.c.) was treated with peroxidase (4 c.c.; 0·6 unit/c.c.) and 20-vol. hydrogen peroxide (2 c.c.). A yellow colour appeared instantly, followed by a turbidity. After 30 min., more hydrogen peroxide (1 c.c.) was added, and at once small needles separated. This solid (0·23 g.) on recrystallisation from aqueous alcohol yielded white needles of 4-hydroxy-3 : 5-dimethylbenzaldehyde, m. p. and mixed m. p. 113—114·5°.

Peroxidase-catalysed Oxidation of Guaiacol.—Guaiacol was purified by distillation and the fraction of b. p. 92°/15 mm. collected: this had m. p. 28—28·75°. Sodium acetate (57·6 g. of monohydrate) and 3N-acetic acid (50 c.c.) were dissolved in water and diluted to 2·5 l.

Guaiacol (10 g.) was dissolved in the buffer (750 c.c.; pH 5) and oxidised by gradual addition of 20-vol. hydrogen peroxide (38 c.c.) and peroxidase (10—14 c.c.; 0·3 unit/c.c.) during 3½ days. An initial brown colour changed to red and then a red oil separated. As the oxidation proceeded a dark red solid settled, and was filtered off and dried (9·5 g.).

Sublimation of oxidation product. The solid melted and the vacuum was increased slowly to avoid bumping as degassing took place. At 140—160°/8 × 10^{-6} mm., a brown crystalline sublimate was obtained. This was resublimed and at 140—160°/2 × 10^{-6} mm. a yellow oil sublimed rapidly and crystallised when rubbed with ether. On filtration of the ethereal slurry, a white solid (20 mg.) of m. p. 124—127·5° remained. Recrystallisation from *cyclo*hexane yielded colourless plates of 2 : 2′-*dihydroxy*-3 : 3′-*dimethoxydiphenyl* (15 mg.), m. p. 141°, mixed m. p. 142·5—143° [Found: C, 68·8; H, 6·2%; *M* (Rast), 227—257. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·8%; *M* 246]. It was soluble in 10% aqueous alkali, being reprecipitated by dilute mineral acid. Concentrated sulphuric acid produced a red-brown colour, which became yellow and finally green. An aqueous solution gave a pale orange-red colour with hydrogen peroxide and peroxidase, or with ferric chloride in the presence of alcohol. With Gibbs's reagent, a blue colour was produced. The infrared absorption spectrum of the compound was identical with that of pure 2 : 2′-dihydroxy-3 : 3′-dimethoxydiphenyl.

Attempted Preparation of 6-Iodoguaiacol.—Guaiacol was converted into 6-nitroguaiacol [31] and then into 6-aminoguaiacol.[32] The amine (0·71 g.) was dissolved in water (5 c.c.), concentrated sulphuric acid (0·33 c.c.) added, and the solution cooled to 0° and diazotised by sodium nitrite solution (0·36 g. in 5 c.c.). Concentrated sulphuric acid (0·25 c.c.) was added and the mixture poured into potassium iodide (1 g.) in water (1 c.c.) at 0°. The mixture was warmed to 70° for 0·5 hr., some tar being produced. It was cooled and extracted with chloroform, and the extract was washed with sodium thiosulphate solution, then with water, and dried ($MgSO_4$). Evaporation yielded a yellow gum which was extracted with light petroleum (b. p. 60—80°),

[30] Fischer and Cammerloher, *Ber.*, 1901, **34**, 948.
[31] Klemenc, *Monatsh.*, 1912, **33**, 702.
[32] Oxford, *J.*, 1926, 2007.

and on evaporation brown crystals (0·184 g.) were obtained. Two sublimations at 80°/0·05 mm. gave orange prisms of *7-methoxybenz-1 : 2 : 3-oxadiazole*, m. p. 102° (Found : C, 55·6, 55·3; H, 4·4, 4·2. $C_7H_6O_2N_2$ requires C, 56·0; H, 4·0%).

2-Methoxy-6-nitrophenyl Toluene-p-sulphonate.—6-Nitroguaiacol (5 g.), heated with toluene-*p*-sulphonyl chloride (10 g.) in pyridine (15 c.c.) at 100° for ½ hr., gave the *toluene-p-sulphonate* (8·9 g., 93%), m. p. 95—95·5° (from methanol) (Found : C, 51·8; H, 4·3; N, 4·4. $C_{14}H_{13}O_6NS$ requires C, 52·0; H, 4·05; N, 4·3%).

2-Amino-6-methoxyphenyl Toluene-p-sulphonate.—The foregoing toluenesulphonate (4·8 g.) was treated in hot acetic acid (10 c.c.) with a warm solution of stannous chloride (12 g. of dihydrate) in concentrated hydrochloric acid (20 c.c.), then heated at 100° for 20 min. to complete reduction; the chlorostannate of the base usually crystallised. Excess of 30% sodium hydroxide solution was added, with cooling and stirring. The white residue was filtered off and dried. Crystallisation from methanol gave colourless prisms of *2-amino-6-methoxyphenyl toluene-p-sulphonate* (2·52 g., 57%), m. p. 117·5—118° (Found : C, 57·4; H, 5·2; N, 4·9. $C_{14}H_{15}O_4NS$ requires C, 57·3; H, 5·2; N, 4·8%).

2-Iodo-6-methoxyphenyl Toluene-p-sulphonate.—2-Amino-6-methoxyphenyl toluene-*p*-sulphonate (0·733 g.) was dissolved in warm concentrated sulphuric acid (0·2 c.c.), and water (5 c.c.) added; the mixture was cooled to 0° and diazotised with sodium nitrite solution (0·1725 g. in 5 c.c.). A red-brown solid separated. Concentrated sulphuric acid (0·1 c.c.) was added, followed by potassium iodide (0·6 g.) in water (2 c.c.). Gas was evolved and brown solid appeared. After 1 hr. at room temperature, the mixture was warmed to 100° to complete the reaction. The solution, containing tar, was extracted with ether; the extract was washed with sodium thiosulphate solution, water, sodium hydroxide solution, and water. Evaporation gave a brown gum which was extracted with hot light petroleum (b. p. 60—80°). The extract gave on evaporation a gum (200 mg.) which solidified on trituration with methanol. Filtration yielded a yellow solid (93 mg.) which was chromatographed in benzene on alumina, the colour being thus removed. The iodo-compound collected in the first benzene eluates, and on evaporation, crystals (85 mg.; m. p. 68—72°) were obtained. Recrystallisation from light petroleum (b. p. 60—80°) gave the *iodo-ester* as prisms (44 mg.), m. p. 84·5—85° (Found : C, 41·3; H, 3·3. $C_{14}H_{13}O_4SI$ requires C, 41·6; H, 3·2%).

3 : 3′-Dimethoxy-2 : 2′-ditoluene-p-sulphonyloxydiphenyl.—Impure iodo-compound (1·71 g.) was heated to 250°, and activated copper bronze [33] (2 g.) was added during 0·5 hr. with stirring. The mixture was then heated at 255° for 20 min., cooled, and extracted with hot methanol (A); the residue was then powdered in a mortar and extracted (Soxhlet) with methanol (B).

Extract A was evaporated, yielding brown amorphous solid (200 mg.), which was extracted with hot light petroleum (b. p. 60—80°) to remove unchanged iodo-compound. The residue, m. p. 140—180°, was adsorbed from benzene on neutral alumina. The column was eluted with benzene and 5 c.c. fractions were collected and evaporated, giving (i) 3·5 mg. the crude diphenyl derivative, m. p. 187—197°; (ii) 24·6 mg. which crystallised from methanol in prisms (14 mg.; m. p. 175—196°); (iii) 29·1 mg. which gave crystals (4 mg.; m. p. 190—200°) from *cyclo*hexane; (iv) material which crystallised from methanol in prisms (7 mg., m. p. 188—202°).

Extract B was evaporated, giving amorphous solid (180 mg.), m. p. 130—190°. This was crystallised twice from aqueous methanol, yielding colourless crystals (30 mg.), m. p. 202—206°. More diphenyl was obtained from the methanolic mother-liquor by chromatography on alumina followed by crystallisation from methanol. The yield of crude 3 : 3′-dimethoxy-2 : 2′-ditoluene-*p*-sulphonyloxydiphenyl was 65 mg. (5%).

The pure crystals from methanol were identical with the solid, m. p. 201—205°, obtained from 2 : 2′-dihydroxy-3 : 3′-dimethoxydiphenyl (prepared by an independent method, see below) and toluene-*p*-sulphonyl chloride.

2 : 2′-Diacetoxy-5 : 5′-diformyl-3 : 3′-dimethoxydiphenyl.—" Dehydrodivanillin " [34] (12 g.) was heated under reflux for 30 min. with acetic anhydride (60 c.c.) and anhydrous sodium acetate (3 g.). The solution was poured into ice-water; a brown oil which separated solidified on scratching (15 g., 98%). Crystallisation from methanol gave colourless crystals, m. p. 113·5—115° (Elbs and Lerch [35] gave m. p. 117°).

2 : 2′-Diacetoxy-3 : 3′-dimethoxydiphenyl-5 : 5′-dicarboxylic Acid.—The diacetyl-dialdehyde (10 g.) in pure acetone (30 c.c.) was oxidised by potassium permanganate (10 g.) in acetone (300 c.c.). After an hour the precipitate was filtered off and suspended in dilute sulphuric acid. Sodium hydrogen sulphite was added to remove manganese dioxide. The white residue was

[33] Kleiderer and Adams, *J. Amer. Chem. Soc.*, 1933, **55**, 4219.
[34] Cf. Tiemann, *Ber.*, 1885, **18**, 3943.

filtered off and washed with water (yield, 7·9 g., 73%). Crystallisation from ethanol gave colourless needles, m. p. 277—278° (decomp.) (Elbs and Lerch [35] gave m. p. 140°) (Found: C, 57·4; H, 4·6; OMe, 14·7; Ac, 21·9. Calc. for $C_{20}H_{18}O_{10}$: C, 57·4; H, 4·3; OMe, 14·8; Ac, 20·6%).

2 : 2′-*Dihydroxy*-3 : 3′-*dimethoxydiphenyl*-5 : 5′-*dicarboxylic Acid*.—The compound (2·2 g.) was refluxed for 1 hr. with 10% aqueous sodium hydroxide, then cooled and acidified with acetic acid. The white precipitate was filtered off, washed with hot ethanol, and dried (1·6 g., 91%). Crystallisation from glacial acetic acid gave clusters of fine needles, m. p. 306—308° (decomp.) (Elbs and Lerch gave m. p. 295°) (Found: C, 57·3; H, 4·4. Calc. for $C_{16}H_{14}O_8$: C, 57·5; H, 4·2%).

2 : 2′-*Dihydroxy*-3 : 3′-*dimethoxydiphenyl*.—2 : 2′-Dihydroxy-3 : 3′-dimethoxydiphenyl-5 : 5′-dicarboxylic acid (430 mg.) was heated to 300°; decomposition then began with evolution of carbon dioxide and blackening. After 20 min., the mixture was cooled and the solid extracted with warm dilute sodium hydroxide solution, which was acidified and extracted with ether. The latter was washed with sodium hydrogen carbonate solution and water and dried (Na_2SO_4). Concentration yielded almost colourless plates of 2 : 2′-*dihydroxy*-3 : 3′-*dimethoxydiphenyl* (136 mg., 43%) which crystallised from *cyclo*hexane as needles, m. p. 142·5—143° (Found: C, 68·6; H, 6·1. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). The diphenyl gave a pale yellow-brown colour with concentrated sulphuric acid, slowly changing to brown. With aqueous-alcoholic ferric chloride solution it gave an orange-red colour. A red colour appeared in its aqueous solution on addition of peroxidase and hydrogen peroxide.

2 : 2′-*Diacetoxy*-3 : 3′-*dimethoxydiphenyl*.—2 : 2′-Dihydroxy-3 : 3′-dimethoxydiphenyl (88 mg.) was heated under reflux for 30 min. with acetic anhydride (5 c.c.) and anhydrous sodium acetate (0·5 g.). The *diacetate* (77 mg., 65%) separated from aqueous methanol as needles, m. p. 133—134° (Found: C, 65·8; H, 5·6. $C_{18}H_{18}O_6$ requires C, 65·5; H, 5·5%).

3 : 3′-*Dimethoxy*-2 : 2′-*ditoluene*-p-*sulphonyloxydiphenyl*.—The diphenol (50 mg.) was heated at 100° with excess of toluene-*p*-sulphonyl chloride in pyridine for 0·5 hr. The mixture was poured into water, and the oil formed was extracted with ether. The extract was washed with dilute hydrochloric acid, sodium carbonate, and sodium hydroxide solutions, and on evaporation gave a gum which crystallised on addition of methanol. Crystallisation from methanol gave 3 : 3′-dimethoxy-2 : 2′-ditoluene-*p*-sulphonyloxydiphenyl (3 mg.), m. p. 201—205°.

Reductive Acetylation of the Guaiacol Oxidation Product.—The product (10·6 g.) was dissolved in acetic anhydride (50 c.c.), giving a deep red solution. Zinc dust (11 g.) and sodium acetate (2 g.) were added, the solution becoming nearly colourless. The reaction was completed under reflux (30 min.). Acetic acid was added and the mixture was boiled and filtered hot, the residue being washed with hot acetic acid. The combined filtrates were poured into cold water; a white solid separated. The yield of mixed acetates, m. p. 75—95°, was 13 g.

The mixture (1·22 g.) was sublimed in a long Pyrex tube. At 5×10^{-5} mm., white crystals sublimed at 180—220°, and at 270° a yellow oil distilled (not examined). The solid, m. p. 90—160°, was purified by repeated fractional sublimation and then crystallised from aqueous methanol as needles (11·3 mg.), m. p. 195·5—197·5° (Fichter and Dietrich [23] gave m. p. 198° for 4 : 4′-diacetoxy-3 : 3′-dimethoxydiphenyl) [Found: C, 65·6; H, 5·8; OMe, 19·5; Ac, 29·4%; *M* (Rast), 340. Calc. for $C_{18}H_{18}O_6$: C, 65·5; H, 5·5; OMe, 18·8; Ac, 26·1%; *M*, 330].

Durenol.—Duridine [35] (7 g.) was dissolved in warm concentrated sulphuric acid (7 c.c.) and water (20 c.c.). Water (60 c.c.) was then added and the solution cooled to 5° and diazotised by slow addition of sodium nitrite solution (3·5 g. in 15 c.c.). The solution was finally warmed to 100° for 20 min.; a pale yellow precipitate of durenol (6·9 g., 98%) separated and was purified by steam-distillation, followed by 2 crystallisations from light petroleum (b. p. 60—80°). The pure durenol was obtained in silvery plates, m. p. 116—117°.

Peroxidase-catalysed Oxidation of Durenol.—Durenol (600 mg.) was dissolved in hot distilled water (2 l.). On cooling rapidly, part of the durenol crystallised in minute needles. Peroxidase (30 c.c.; 0·6 unit/c.c.) and 20-vol. hydrogen peroxide (26 c.c.) were added in small amounts, at intervals, during 5 days. No colour changes were observed. The solution was filtered and the precipitate (308 mg.) and filtrate were examined.

The dry precipitate (m. p. 106—160°; 240 mg.) was sublimed at 70—80°/40—50 mm. Unchanged durenol (100 mg.) was recovered and the residue crystallised from aqueous methanol and then from light petroleum (b. p. 60—80°), giving colourless prisms (41 mg.) of 4 : 4′-*dihydroxy*-2 : 3 : 5 : 6 : 2′ : 3′ : 5′ : 6′-*octamethyldiphenyl*, m. p. 197—198·5° [Found: C, 80·7; H, 8·6%;

[35] Birtles and Hampson, *J.*, 1937, 10.

M (Rast), 300. $C_{28}H_{24}O_2$ requires C, 80·5; 8·8%; *M*, 298]. The *diacetate* (30·4 mg.), prepared by use of acetic anhydride and sodium acetate and crystallised from methanol, had m. p. 179—180° (Found: C, 75·4; H, 8·2. $C_{34}H_{30}O_4$ requires C, 75·3; H, 7·9%).

The filtrate was extracted with ether. Evaporation of the dried extracts yielded a gum (274 mg.). Sublimation at 80—90°/40—50 mm. gave yellow crystals (2 mg.; m. p. 105—107°) with a quinone-like smell. This compound was duroquinone, as shown by comparison of the infrared absorption spectrum with that of authentic duroquinone. An *X*-ray diffraction photograph gave the length of one side of the unit cell as 6·9 Å, the same as that of the authentic quinone.

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199. *The Stereochemistry of Sesquiethylenediaminetrimethylplatinic Iodide.*

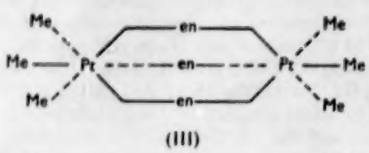
By MARY R. TRUTER and (in part) E. G. COX.

Sesquiethylenediaminetrimethylplatinic iodide has been shown by *X*-ray crystal-structure analysis to contain the cation $[en\ (CH_3)_3Pt\ en\ Pt(CH_3)_3\ en]^{2+}$. The two halves of the ion are related by a 2-fold axis perpendicular to the C–C bond of the bridging ethylenediamine molecule. Each platinum atom is surrounded octahedrally by three nitrogen and three carbon atoms in the *cis*-configuration of the type PtA_3X_3.

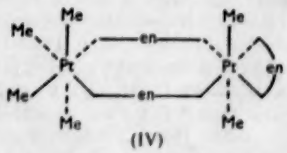
SESQUIETHYLENEDIAMINETRIMETHYLPLATINIC IODIDE, empirical formula $Pt(CH_3)_3I,1\frac{1}{2}en$ (en = ethylenediamine), was first prepared by Lile and Menzies.[1] The molecule must clearly contain at least two platinum atoms, and, as Lile and Menzies suggested,[2] its most likely formation is as a complex salt (I), in the positive ion of which the platinum atoms would be held together by one or more ethylenediamine groups and each have an octahedral

(I) $[Pt_2Me_6\ en_3]I_2$ $[PtMe_4][Pt\ en_2]I_2$ (II)

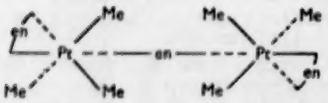
configuration. The formation of polynuclear structures by means of halogen or methyl bridges such as occur in trimethylplatinic chloride and tetramethylplatinum [3] is extremely



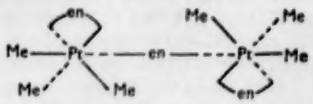
(III)



(IV)



(V)



(VI)

unlikely, but the structure (II), cannot be entirely be excluded. The *X*-ray investigation reported in this paper was undertaken to discriminate between this structure (II) and the various stereochemical forms of structure (I).

[1] Lile and Menzies, *J.*, 1949, 1168; W. J. Lile, Thesis, Bristol, 1937.
[2] Cf. Foss and Gibson, *J.*, 1951, 299.
[3] Rundle and Sturdivant, *J. Amer. Chem. Soc.*, 1947, **69**, 1561.

Not counting enantiomers there are eight possible isomers of structure (I)—one with three en bridges, two with two bridges, and five with one bridge; of these, however, only (III), (IV), (V), and (VI), together with (II), satisfy the requirement which emerged from the preliminary *X*-ray examination, that the molecule must have at least a two-fold axis of symmetry. While further discrimination could be effected by finding the positions of the platinum atoms, a detailed analysis has been necessary to determine the structure finally; notwithstanding the large scattering power of platinum and iodine it has been possible to locate all the carbon and nitrogen atoms unequivocally and thereby to show that the structure is (VI).

Experimental

The sample was prepared and analysed by Messrs. Johnson Matthey and Co. [Found: Pt, 42·6. Calc. for $Pt_2en_3(CH_3)_4I_2$: Pt, 42·7%]. The acicular crystals were set up about the needle axis [001], and rotation and Weissenberg photographs were taken with Cu-K_α radiation. The unit cell dimensions are $a = 16{\cdot}54 \pm 0{\cdot}01$, $b = 12{\cdot}10 \pm 0{\cdot}01$, $c = 12{\cdot}92 \pm 0{\cdot}05$ Å; the value for c was obtained by measurement of a rotation photograph, and the other two by Straumanis's method (approximate values having been obtained from Weissenberg photographs). The measured volume, 2586 Å^3, with 4 molecules (M, 914) per unit cell gives a calculated density of 2·38. It was not possible to measure the density of the iodide because the small crystals dissolved in both aqueous and organic liquids; however the density of the nitrate, $Pt_2en_3Me_6(NO_3)_2$, determined by flotation in cadmium borotungstate solution, was 2·12, so that 2·38 is a reasonable value for the iodide.

The following classes of reflections were found to be systematically absent: hkl when $h + k + l = 2n + 1$; $0kl$ when $k = 2n + 1$ ($l = 2n + 1$); $h0l$ when $h = 2n + 1$ ($l = 2n + 1$). Hence the space group is either (i) $Iba - C_{2v}^{21}$ or (ii) $Ibam - D_{2h}^{26}$, the molecular symmetry required being (i) 2 or (ii) 222 or 2/*m*.

Weissenberg photographs of the ($hk0$) zone were taken by a multiple-film technique. Of a possible 128 reflections, 100 were observed and their intensities estimated visually by comparison with a calibration slip; Lorentz and polarisation corrections were applied, giving a set of relative values of F^2. Approximately absolute values and temperature factors were determined by Wilson's method. The intensities were redetermined by a different observer and the agreement $\sum|\Delta F|/\sum F$ between the two sets was 0·073.

No absorption correction was made. The crystal approximated to a cylinder 0·01 mm. in diameter and 1·0 mm. long; the linear absorption coefficient is 425 cm.$^{-1}$.

Structure determination.

In either possible space group the molecules (or constituent ions) of sesquiethylenediaminetrimethylplatinic iodide must occupy special positions, in *Ibam* with symmetry 222 (three two-fold axes) or 2/*m* (two-fold axis and plane) and in *Iba* with symmetry 2 (two-fold axis). In form (IV) the two-fold symmetry axis must pass through both platinum atoms, whereas in (III), (V), and (VI) it must be perpendicular to the line joining them; form (IV) can therefore be rejected because it is impossible to accommodate two molecules end-to-end along the Pt–Pt direction in a c-axis of only 13 Å, as would be required by the symmetry. The possible symmetries, positions of the platinum atoms, and corresponding Patterson peaks in an $hk0$ projection for the other stereochemical forms are as follows:

Form.	Symmetry		Pt co-ordinates		Patterson Pt peaks in projection
	Ibam	*Iba*	*Ibam*	*Iba*	
(II)	222	2	0, 0, ½, etc. and ½, 0, ½, etc.	00z, etc. and 0, ½, z', etc.	0, ½; ½, 0
(III)	—	2	—	xyz, etc.	$2x$, $2y$; $2x$, 0; 0, $2y$
(V)	2/*m*	2	x, y, 0, etc.	xyz, etc.	$2x$, $2y$; $2x$, 0; 0, $2y$
(VI)	—	2	—	xyz, etc.	$2x$, $2y$; $2x$, 0; 0, $2y$

The Table shows that the location of the platinum peaks in an ($hk0$) Patterson projection will discriminate between form (II) on the one hand and (III), (V), and (VI) on the other, but that further information will be necessary to distinguish between the last three.

FIG. 1. *Electron density projection along [001], the contours are at 10e/Å² intervals, the zero contour is dotted.*

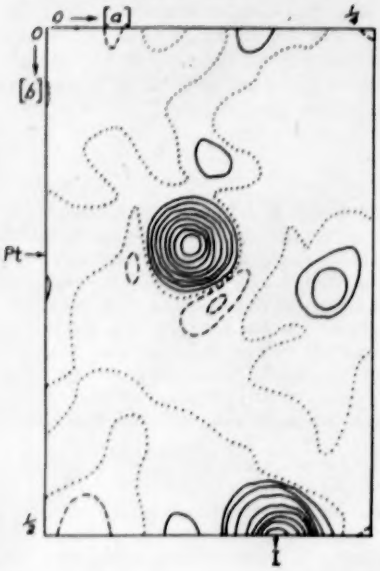


FIG. 2. *Electron density difference ($\rho_o - \rho_c$) projected along [001], contours at 4e/Å², negative contours dashed, zero dotted.*

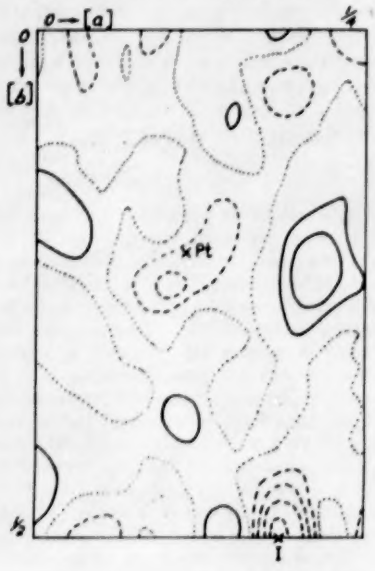
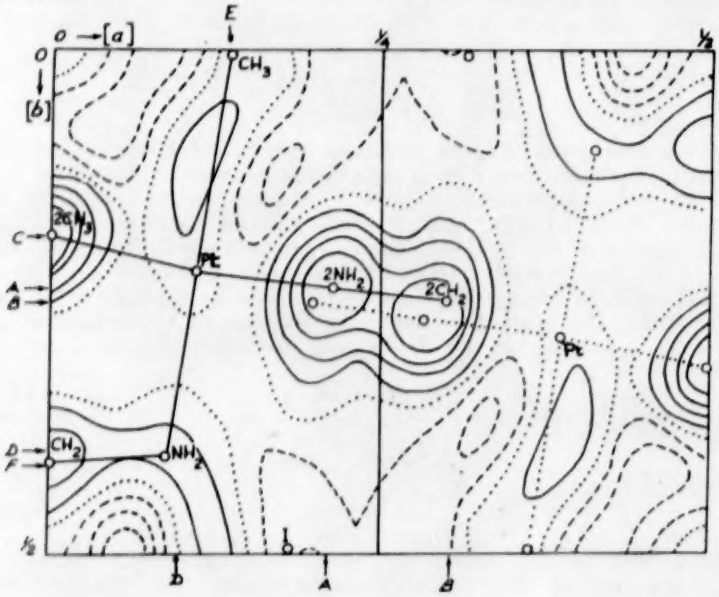


FIG. 3. *Electron density difference ($\rho_o - \rho_c$) projected along [001] calculated from reflections with sin θ <0·5. Positive contours full lines, zero dotted lines, negative contours dashed lines, at arbitrary equal intervals.*



An (*hk*0) Patterson projection was computed and gave a consistent set of Pt–Pt peaks at 0,2*y*, 2*x*,0, and 2*x*,2*y*, with $x = 0{\cdot}110$, $y = 0{\cdot}215$, and Pt–I and I–I peaks corresponding to iodine atoms at $x = 0{\cdot}18$ and $y = 0{\cdot}50$. There are no peaks at $0,\frac{1}{2}$, so that the structure (II) can be eliminated. Discrimination between the other possibilities would be effected only by finding the carbon and nitrogen atoms and since it was hardly to be expected that these could be located from a Patterson synthesis, it was now necessary to compute Fourier syntheses, in the first instance on the assumption that the signs of all the terms were determined by the contributions of the platinum and the iodine atoms. Some structure factors were calculated from the co-ordinates given above, with the scattering factors for platinum and iodine from the International Tables multiplied by a temperature factor $\exp -B(\sin^2\theta)/\lambda^2$ with $B = 2{\cdot}0 \times 10^{-16}$ cm.^{2}; this value of B was obtained by Wilson's method.[4] Reasonable agreement with the observed structure factors was obtained, so the signs of all F's were calculated from the Patterson co-ordinates and used with the observed amplitudes to carry out a Fourier synthesis. The resulting projection of the electron density is shown in Fig. 1; the positions of the maxima are Pt at 0·112, 0·218, and I at 0·184, 0·500, the latter peak being due to the overlapping of two iodide ions at x,y,z and $x,y,\frac{1}{2}+z$, with y nearly $\frac{1}{4}$. The low density in the regions near 0,0 and $0,\frac{1}{2}$ indicates that a triple ethylenediamine bridge is unlikely while the high density at about $\frac{1}{4},\frac{1}{4}$ is consistent with a non-bridging chelate ethylenediamine so that although individual light atoms are not yet clearly shown this preliminary glimpse suggests configuration (V) or (VI).

In the hope of resolving the light atoms a difference synthesis (in which the coefficients were observed structure amplitudes minus amplitudes calculated for platinum and iodine only) was calculated, the signs being determined by the Pt and I co-ordinates from the Fourier map except that y_I was arbitrarily taken to be 0·490. The most important feature in the resulting (ρ_0–ρ_c) map (Fig. 2) is the negative region ($\rho_0 < \rho_c$) round the iodine position; there is no trace of the positive peak to be expected if further removal from $y = \frac{1}{4}$ is required, and the explanation must be that the temperature factor of the iodine is too low; examination of Fig. 1 also shows an electron density for the superimposed iodide ions lower than that to be expected from a comparison with the platinum peak. Accordingly, for the subsequent calculations, the B factor for iodine was assumed to be 3·0; values of $B = 2{\cdot}0$ and $B = 3{\cdot}0$ for platinum and iodine respectively correspond to r.m.s. displacements of 0·16 and 0·195 Å, which are almost exactly in the ratio, 0·81, to be expected from the atomic masses.

Fig. 2, although still not showing the light atoms very clearly, indicates the need for small shifts of the platinum and iodine atoms, and the co-ordinates finally adopted were: Pt, $x = 0{\cdot}111$, $y = 0{\cdot}216$; I, $x = 0{\cdot}181$, $y = 0{\cdot}495$; the last co-ordinate was chosen after calculations by trial and error with the (0*k*0) planes. The agreement index $R = \sum|F_o - F_c|/\sum|F_o|$ at this stage was 0·20.

Although the value of R calculated for all planes was 0·20, that for planes with $\sin\theta < 0{\cdot}5$ was 0·25 and that for planes with $\sin\theta > 0{\cdot}5$ was 0·16, in complete contrast to the normal increase of R with $\sin\theta$. This was clearly due to the fact that the light atoms, not yet allowed for in the calculated F's, make a much larger contribution to the low-order than to high-order planes. Accordingly, an (*hk*0) difference synthesis was calculated with F's for planes having $\sin\theta < 0{\cdot}5$ only, with the result (Fig. 3) that light atom peaks appeared clearly.

The large peaks *A*, *B*, and *C* evidently each represent more than one atom and it was assumed that *A* and *B* were due to non-bridging ethylenediamine molecules viewed edge-on in the projection as shown. In addition, after preliminary trials of other possibilities which gave less good agreement, *C* was taken to be two methyl groups attached to the same platinum atom, and overlapping in projection. If the platinum valencies were octahedral there should be atoms at approximately *D* and *E*, and of these evidently *D* is the nitrogen of the bridging ethylenediamine and *F* is the CH_2 of this bridge (the 2-fold axis of the molecule is thus at $0,\frac{1}{4},z$). With these assumptions and some adjustments of the atomic positions in detail the agreement index was reduced to $R = 0{\cdot}118$ for (*hk*0) planes with

[4] Wilson, *Acta Cryst.*, 1949, **2**, 318.

Comparison of observed and calculated structure factors.

hkl	$F_{obs.}$	$F_{calc.}$	*hkl*	$F_{obs.}$	$F_{calc.}$	*hkl*	$F_{obs.}$	$F_{calc.}$	*hkl*	$F_{obs.}$	$F_{calc.}$
000	—	(1624)	060	87	− 79	110	105	− 85	170	359	−381
200	196	−170	260	150	−125	310	266	270	370	394	420
400	496	−434	460	81	51	510	355	−368	570	167	144
600	55	83	660	251	274	710	62	76	970	239	−193
800	184	114	860	255	−203	910	234	257	11,7,0	147	−170
10,0,0	469	478	10,6,0	81	− 54	11,1,0	200	−218	13,7,0	299	298
12,0,0	159	− 88	12,6,0	134	132				15,7,0	134	124
14,0,0	302	−342				130	416	−454	17,7,0	159	−193
18,0,0	204	202	080	164	160	330	402	415			
			280	214	−227	530	80	− 69	190	164	170
020	334	−271	680	163	139	730	50	− 27	590	344	−366
220	206	−226	880	207	−223	930	139	−116	790	88	43
420	238	279				11,3,0	182	265	990	299	336
620	463	463	0,10,0	310	293	13,3,0	210	233	11,9,0	83	− 94
820	430	−504	4,10,0	182	−181	15,3,0	123	80	13,9,0	139	−124
10,2,0	230	−251	10,10,0	134	110	17,3,0	128	−201	15,9,0	74	− 55
12,2,0	283	282	14,10,0	155	−166				17,9,0	43	45
14,2,0	146	58				150	285	282			
18,2,0	178	−197	0,12,0	98	− 43	350	125	80	1,11,0	195	−180
			2,12,0	131	−109	550	498	−585	3,11,0	215	240
040	620	772	4,12,0	144	160	750	67	94	5,11,0	101	74
240	262	−259	6,12,0	155	170	950	420	498	9,11,0	115	− 82
440	293	−312	8,12,0	200	−212	11,5,0	81	− 94	13,11,0	130	165
640	125	104	10,12,0	94	− 62	13,5,0	166	−101			
10,4,0	259	276	12,12,0	92	92	15,5,0	101	− 47	5,13,0	150	−127
12,4,0	119	− 85				17,5,0	105	50	9,13,0	101	107
14,4,0	200	−251	0,14,0	250	233						
18,4,0	121	111	4,14,0	179	−185						

sin $\theta < 0{\cdot}5$ and $R = 0{\cdot}143$ for all (*hk*0) planes. A table of observed and calculated structure) factors is given.) This very substantial improvement in R leaves no doubt as to the correctness of the assigned structure which is (VI), *i.e.*, one in which each platinum atom has *cis*-configuration of the attached C_3N_3. The final fractional co-ordinates are :

	Pt	I	2N (peak A)	2C (peak B)	2Me (peak C)	Me (peak E)	N (bridge)	C (bridge)
x	0·111	0·181	0·213	0·298	0·000	0·135	0·088	0·000
y	0·216	0·495	0·231	0·252	0·184	0·015	0·408	0·436

Owing to overlap in the projection the Pt–C and Pt–N distances cannot be considered to be very accurate, but their average value is 2·45 Å which is in agreement with accepted values. The Pt–Pt distance is 7·79 Å.

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200. *Liquid-phase Reactions at High Pressures. Part X.* The Rates of Some Isomerisations and Rearrangements.*

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The rates of five isomerisations and rearrangements in solution have been measured at pressures up to 5000 atmospheres. One of the reactions is slowed by high pressures and the other four are accelerated, but to widely varying degrees. The differences in the response to pressure can be explained on the basis of the ionic solvation theory of the pressure effect, except in the case of the cyclisation of citraldehyde. The acceleration of this reaction probably indicates that the configuration necessary for ring-formation is favoured by high pressures.

The investigation of the effect of high pressures on the rates of reactions in liquids and solutions has been extended to some isomerisations and molecular rearrangements. Rate determinations have been made up to 5000 atm. and usually at several temperatures, for (i) the isomerisation of maleic acid to fumaric acid, catalysed in aqueous solution by potassium thiocyanate, (ii) the isomerisation of diethyl maleate to diethyl fumarate in acetone, catalysed by diethylamine, (iii) the rearrangement of *N*-chloroacetanilide to *o*- and *p*-chloroacetanilide, catalysed by hydrochloric acid, in aqueous solution, (iv) the rearrangement of α-phenylallyl alcohol to cinnamyl alcohol in aqueous dioxan, catalysed by hydrochloric acid, and (v) the cyclisation of citraldehyde to *p*-menth-1-ene-3 : 8-diol, catalysed by hydrochloric acid in aqueous ethanol.

Experimental

Apparatus.—The high-pressure equipment has been described in earlier papers.[1] The cylindrical steel vessel is immersed in an oil-bath at a constant temperature (±0·05°), and is closed at the top by a steel screw plug. The lower end of the cylinder is connected by steel capillary tubing to a piston intensifier. The apparatus contains medicinal paraffin and the pressure is transmitted to the reactants through a mercury seal at the bottom of the Pyrex glass reaction tube of 3 to 4 ml. capacity.

Procedure.—Solutions of reactant and catalyst of concentrations chosen to give a time of half-change between four and seven hours were mixed and put in the reaction tube. This was enclosed in the pressure vessel and pressure was generated through the intensifier by means of an oil hand-pump. The pressure on the low-pressure side of the intensifier was measured on a Bourdon tube gauge (calibrated against a free-piston gauge) and the pressure in the reaction vessel was calculated from the known effective ratio of the intensifier. Throughout the runs (250 to 500 min.) the pressure was kept constant (±1%).

Materials.—Potassium thiocyanate, hydrochloric acid, acetone, and dioxan of "AnalaR" grade, and absolute ethanol were used. Diethylamine (b. p. 55·5°/755 mm.) and α-citraldehyde (b. p. 118°/20 mm., n_D^{17} 1·4895) were redistilled. Maleic acid (m. p. 131°) was prepared by dissolving redistilled maleic anhydride (b. p. 84°/15 mm.) in water, recrystallising twice, and drying *in vacuo*. Diethyl maleate (b. p. 120°/25 mm., $n_D^{17\cdot5}$ 1·4409) and diethyl fumarate (b. p. 106°/25 mm., $n_D^{17\cdot5}$ 1·4420) were prepared from ethanol and the acids.[2] α-Phenylallyl alcohol (b. p. 106°/16 mm., $n_D^{17\cdot6}$ 1·5442) was prepared from acraldehyde and phenylmagnesium bromide.[3] *N*-Chloroacetanilide was made from acetanilide and sodium hypochlorite[4] and was 99·5% pure (titration of iodine liberated from potassium iodide). Solutions of the reactants were stored in the dark.

Analytical Methods.—Reaction (i). Maleic acid solution (2 ml.) and potassium thiocyanate solution (1 ml.) were pipetted into the reaction tube, and Terry and Eichelberger's analytical method[5] was used. Fumaric acid was precipitated at 0°, and the unchanged maleic acid titrated with sodium hydroxide (phenolphthalein).

* Part IX, *J.*, 1955, 2295.

[1] (*a*) P'eng, Sapiro, Linstead, and Newitt, *J.*, 1938, 784; (*b*) Weale, *J.*, 1954, 2959.
[2] Wachholtz, *Z. phys. Chem.*, 1927, **125**, 1.
[3] Braude, Jones, and Stern, *J.*, 1946, 396.
[4] Barnes and Porter, *J. Amer. Chem. Soc.*, 1930, **52**, 1721.
[5] Terry and Eichelberger, *ibid.*, 1925, **47**, 1402.

Reaction (ii). Nozaki's modification [6] of Kistiakowsky and Smith's [7] method was employed. After removal of solvent and catalyst, 0·40 ml. of the partially isomerised ester was added to 0·60 ml. of liquid paraffin and the consolute temperature determined. The composition was then obtained (±0·5%) from the linear relation between consolute temperature and composition found experimentally (100% maleate, 105·1°; 100% fumarate, 30·0°).

Reaction (iii). *N*-Chloroacetanilide was determined by titration with thiosulphate of the iodine liberated from 2 ml. of reaction mixture by 20 ml. of 0·1N-potassium iodide containing acetic acid.

Reaction (iv). As in the method of Braude *et al.*,[3] the change in absorption at 251 mμ was measured with a Unicam ultraviolet spectrophotometer. Considerable care was necessary with the acetone solutions as this solvent absorbs appreciably at 251 mμ.

Reaction (v). The rate of the cyclisation of citraldehyde, which is accompanied by disappearance of the aldehyde group and one of the two double bonds, was measured in water by Price and Dickman.[8] Aqueous ethanol, in which citraldehyde is more soluble, was used in the high-pressure experiments because of the small volume of the reaction tube. The reaction was followed by quantitative bromination. To 1 ml. of the reacting solution was added a measured excess of freshly standardised bromine water, and the mixture kept for 2 min. Excess of potassium iodide solution was then added and the iodine titrated with thiosulphate. Three such determinations were performed in succession, and the bromine water was immediately re-standardised.

Experiments without Catalyst.—Subsidiary experiments showed that none of the reactions proceeded at a measurable rate under pressure without a catalyst. Diethyl maleate containing diethylamine, but without solvent, underwent 100% isomerisation in less than 1 hr.

Results.—With the possible exception of the isomerisation of maleic acid, previous workers have established that at normal pressure the reactions are of the first order with respect to the substance undergoing rearrangement.[3, 6, 8, 9, 10, 11] It has also been shown that the observed reaction constants, k', contain the catalyst activity (in two cases the square of the activity) as a factor. To have systematically confirmed these findings at high pressures would have been prohibitively time-consuming, but the rate constants for each reaction, calculated according to the normal-pressure kinetics from runs of varying duration, were satisfactorily consistent.

Each of the observed constants, k', should therefore be divided by the appropriate power of the catalyst activity at the pressure and temperature of the measurement, to convert it into the true first-order constant, k. If this is not done the effect of pressure on the rate may be obscured by changes in the activity of the catalyst at high pressures. Except for aqueous dioxan solutions the actual catalyst concentrations can be calculated from existing data for the compressions of the solvents. An expression for the activity coefficients of hydrochloric acid in water at high pressures is given by Harned and Owen [12] so that the complete correction can be made for the *N*-chloroacetanilide rearrangement. Although only the concentration correction has been applied to the other reactions, the effect of pressure on the activity coefficients of the catalysts will usually be of a lower order of magnitude than the effect of pressure on k, and inability to allow for it will not change the general conclusions.

The absolute values of k for these reactions would be different if accurate activity coefficients were available. From data at 1 atm.[13] it is estimated that the approximate activity coefficients of the catalysts in the solvents employed for the cyclisation of citraldehyde at 25°, the isomerisation of maleic acid at 79·8°, and the allylic rearrangement in aqueous dioxan at 30° and 50° (for which solvent there are no compression data) are respectively 0·66, 0·7, 0·4, and 0·35. The values of k in Table 1 for these reactions would therefore be greater by factors of about 1·5, 1·4, 2·5, and 2·9 if the complete correction could be made.

For calculation of the catalyst concentration in water and in acetone Bridgman's compression data [14] were used, those for acetone being smoothed by use of Hudleston's relationship.[15]

[6] Nozaki, *J. Amer. Chem. Soc.*, 1941, **63**, 2681.
[7] Kistiakowsky and Smith, *ibid.*, 1934, **56**, 638.
[8] Price and Dickman, *Ind. Eng. Chem.*, 1948, **40**, 257.
[9] Nozaki and Ogg, *J. Amer. Chem. Soc.*, 1941, **63**, 2583.
[10] Harned and Seltz, *ibid.*, 1922, **44**, 1475.
[11] Percival and La Mer, *ibid.*, 1936, **58**, 2413.
[12] Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd Edn., Reinhold, New York, 1950, p. 378.
[13] Ref. 12, pp. 548—563.
[14] Bridgman, *Proc. Amer. Acad. Arts Sci.*, 1912, **48**, 309; 1913, **49**, 1.
[15] Hudleston, *Trans Faraday Soc.*, 1937, **33**, 97. Cf. (*a*) Newitt and Weale, *J.*, 1951, 3092; (*b*) Bett, Weale, and Newitt, *Brit. J. Appl. Phys.*, 1954, **5**, 243.

Moesveld's values [16] for aqueous ethanol were also extrapolated by this method, and the compressions of aqueous acetone were calculated from those of the pure components, as they are nearly additive at the composition used.[16a]

The method of converting the observed first order constant, k' (sec.$^{-1}$), to the corrected constant, k, is indicated for each reaction in Table 1. Concentrations are in moles litre^{-1}, C is

TABLE 1. *Rate constants of the isomerisations and rearrangements.*

(i) Isomerisation of maleic acid in water catalysed by potassium thiocyanate.

$k = k'/C$, $C_0 = 0{\cdot}0893$, [maleic acid] = 1·3—1·5.

Temp.	P	10^4k	k_p/k_1
79·8°	1	2·82	1·0
,,	1000	3·46	1·2
,,	3000	5·02	1·78
,,	4900	6·98	2·48

(Second-order rate constant, 10^4k_2 = 3·77, 4·52, 6·40, 9·13).

(ii) Isomerisation of diethyl maleate in acetone catalysed by diethylamine.

$k = k'/C^2$, $C_0 = 0{\cdot}0216$, [diethyl maleate] = 1·105.

25°	1	84·5	1·0
,,	1500	270	3·2
,,	3000	628	7·43
30	1	110	1·0
,,	3000	895	8·13
35	1	141	1·0
,,	500	180	1·28
,,	1000	325	2·31
,,	2000	623	4·43
,,	3000	1170	8·30

(iii) Rearrangement of *N*-chloroacetanilide in water catalysed by hydrochloric acid.

$k = k'/a_{H^+}a_{Cl^-} = k'/a_{HCl}^2$, $C_0 = 0{\cdot}1$, [*N*-chloroacetanilide] = 0·005.

25°	1	27·3	1·0
,,	1500	18·0	0·66
,,	2000	15·6	0·57
,,	3000	13·9	0·51
,,	5000	11·9	0·44
35	1	88·2	1·0
,,	2000	49·2	0·56
,,	3000	40·0	0·45
,,	5000	30·7	0·35

(iv) Rearrangement of α-phenylallyl alcohol: (*a*) in aqueous acetone (45·7 wt. % Me_2CO) catalysed by hydrochloric acid.

$k = k'/C$, $C_0 = 0{\cdot}05$. Concn. of alcohol, 0·0782% (w/v).

Temp.	P	10^4k	k_p/k_1
30·0°	1	1·03	1·0
,,	2000	1·51	1·47
,,	4000	1·64	1·59
35·6	1	2·32	1·0
,,	1000	2·92	1·26
,,	2000	3·57	1·54
,,	4000	3·88	1·67
40·0	1	4·05	1·0
,,	1000	5·05	1·25
,,	2000	5·97	1·47
,,	4000	6·75	1·67
45·4	1	8·38	—

(*b*) in aqueous dioxan (60% v/v). (Constants not corrected for catalyst concentrations or activity coefficients.)

$C_0 = 0{\cdot}08$. Concn. of alcohol, 0·0979% (w/v).

30·0	1	0·0498	—
,,	1000	0·0545	1·09
36·3	1	0·0942	—
,,	1000	0·108	1·14
43·1	1	0·225	—
50·0	1	0·462	—
,,	1000	0·570	1·23

(v) Cyclisation of citraldehyde in aqueous ethanol (44·1 wt. % EtOH) catalysed by hydrochloric acid.

$k = k'/c$, $C_0 = 0{\cdot}1$, [citraldehyde] $\simeq 0{\cdot}025$.

25·2°	1	0·912	1·0
,,	1000	2·28	2·5
,,	2000	4·43	4·9
,,	3000	6·73	7·4
,,	4000	7·88	8·6
,,	5000	8·57	9·4
30·0	1	1·22	1·0
,,	1000	3·17	2·6
,,	2000	5·70	4·7
,,	3000	8·58	7·0
,,	4000	10·3	8·4
,,	5000	10·6	8·7
35·4	1	1·85	1·0
,,	1000	4·55	2·5
,,	2000	7·65	4·1
,,	3000	11·3	6·1
,,	4000	13·1	7·1

the catalyst concentration at the appropriate pressure and temperature, while C_0 is that at 1 atm. and 20°; the reactant concentrations also refer to this temperature and pressure. P is the pressure in atmospheres (1 atm. = 1·0133 bars = 1·0322 kg./cm.^{2}), and k_p/k_1 is the ratio of the rate at P to that at ordinary pressure.

The isomerisation of maleic acid was measured only at 79·8° because the pressure effect was small and there was a tendency for fumaric acid to precipitate during runs at lower temperatures. The Arrhenius parameters of the other reactions, obtained from the graphs of

[16] Moesveld, *Z. phys. Chem.*, 1923, **105**, 450.

TABLE 2. *The Arrhenius parameters of the rearrangements.*

P	E (kcal. mole^{-1})	$\log_{10} A$
(ii) Diethyl maleate (in acetone)		
1	9·3	4·75
3000	10·7	6·7
(iii) *N*-Chloroacetanilide (in water)		
1	21·3 *	13·1
2000	21·0 *	12·6
3000	19·3 *	11·3
5000	17·3 *	9·7
(iv) α-Phenylallyl alcohol (in aqueous acetone)		
1	26·3	15·0
1000	23·7 *	13·2
2000	26·4	15·2
4000	26·7	15·4
(iv) α-Phenylallyl alcohol (in aqueous dioxan) †		
1	22·5	10·8
1000	22·9	11·2
(v) Citraldehyde (in aqueous ethanol)		
1	12·5	5·1
1000	11·9	5·1
2000	9·6	3·7
3000	8·9	3·2
4000	8·8	3·4

* From rates at only two temperatures. † Calc. from k'.

$\log_{10} k$ against $1/T$, are given in Table 2. Only in the case of *N*-chloroacetanilide are the values of A corrected for the activity coefficient of the catalyst.

Where comparison can be made the results at 1 atm. agree satisfactorily with previously recorded values. The maleic acid reaction (see p. 958) is represented slightly better by first-order than second-order constants, but both are shown in Table 1 and are in agreement, at 1 atm., with Nozaki and Ogg's values [9] of $2{\cdot}77 \times 10^{-4}$ and $3{\cdot}87 \times 10^{-4}$ (sec.$^{-1}$) respectively. The value of k_p/k_1 is little influenced by the choice of first- or second-order constants. The rate constants and the activation energy of the rearrangement of *N*-chloroacetanilide at 1 atm. agree with the values $2{\cdot}65 \times 10^{-3}$, $8{\cdot}68 \times 10^{-3}$ (sec.$^{-1}$), and 21·57 calculated from Harned and Seltz's results [10] (see also Percival and La Mer,[11]) at the same temperatures and catalyst concentration. The results for the allylic rearrangement in aqueous dioxan accord reasonably well with those of Braude *et al.*[3] for a somewhat higher catalyst concentration, and the activation energy of the isomerisation of diethyl maleate in acetone is similar to the value of 9·94 kcal. measured in ether by Nozaki.[6] Because of the difference in solvent and catalyst concentration the results for the cyclisation of citraldehyde cannot be compared with those of Price and Dickman.[8]

DISCUSSION

The dependence of the rates of reactions in liquids on pressure has been related to the volume change, ΔV^*, which accompanies formation of the transition state by the equation [17] $\partial \log k/\partial P = -\Delta V^*/RT$. ΔV^* can be obtained from the slopes of the $\log k_p/k_1$–P isotherms (Figure). As Table 3 shows, ΔV^* is positive for the *N*-chloroacetanilide reaction,

TABLE 3. *Volume changes for transition-state formation,* ΔV^* *(c.c./mole).*

	Temp.	P (atm.) 1	1000	2000	3000	4000	5000
(i) Maleic acid	79·8°						−5·44, −5·18 *
(ii) Diethyl maleate	25	−22·9	−16·0	−14·5	−12·7		
	35	−25·4	−18·7	−15·8	−14·6		
(iii) *N*-Chloroacetanilide	25	7·2	6·7	5·2	3·0	2·0	1·0
	35	8·1	7·7	6·4	4·4	3·3	2·6
(iv) α-Phenylallyl alcohol (aq. acetone)	30	−5·0	−5·0	−2·9	−1·6	−1·0	
	35·6	−6·1	−5·1	−2·9	−1·6	−1·0	
	40	−6·2	−5·2	−3·0	−1·6	−1·0	
(iv) α-Phenylallyl alcohol (aq. dioxan)	30		−3·24 †				
(v) Citraldehyde	25·2	−24·5	−20·1	−13·8	−5·6	−2·5	−1·3
	30	−25·8	−17·1	−12·4	−8·4	−1·6	−0·4
	35·4	−26·2	−16·3	−11·8	−6·9	−0·6	—

* From 1 to 5000 atm., first- and second-order respectively.
† From 1 to 1000 atm., from uncorrected constants.

which is retarded by pressure, and is negative for the other reactions but varies considerably from one to another. For the isomerisations of maleic acid, and of diethyl maleate in ether, ΔV^* is independent of pressure.

Buchanan and Hamann [18] have recently presented new evidence that, if ionic charges appear or disappear during the rate-determining step, the sign of ΔV^* (respectively

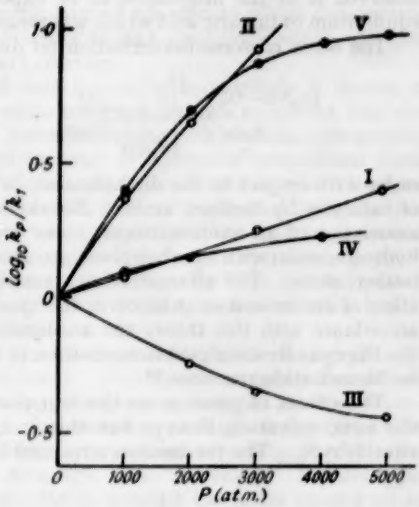
[17] Evans and Polanyi, *Trans. Faraday Soc.*, 1935, **31**, 875; 1936, **32**, 1333.
[18] Buchanan and Hamann, *ibid.*, 1953, **49**, 1425.

negative or positive) is determined by this characteristic. In such reactions ΔV^* is largely accounted for by the electrostriction or liberation of neighbouring molecules, and at high pressures there is a reduction of the free energy of ionic solvation which is part of the free energy of activation. A quantitative estimate of the effect is possible for some reactions, if the appropriate ionic equilibria have been measured at high pressures, and there should exist a general correlation between pressure-reponse and electrical charge-type.

Although the rearrangement of *N*-chloroacetanilide does not result in a net gain or loss of ionic charge, the rate-determining stage (HCl catalyst) is

$$\overset{+}{\text{Ph}}\cdot\text{NHCl}\cdot\text{Ac} + \text{Cl}^- \longrightarrow \text{Ph}\cdot\text{NH}\cdot\text{Ac} + \text{Cl}_2$$

which is followed by chlorination of the acetanilide.[19] In this stage two charges disappear and the liberation of electrostricted solvent molecules will cause ΔV^* to be positive. The

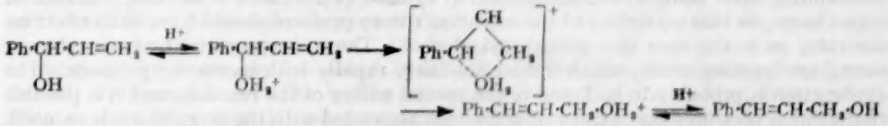


Relative reaction rates.

I, Maleic acid (79·8°); II, diethyl maleate (35°); III, *N*-chloroacetanilide (35°); IV, α-phenylallyl alcohol (40°); V, citraldehyde (25·2°).

retarding effect of pressure, found experimentally, is thus predictable from the charge-type. It is comparable with the retardation of the decomposition of allylbenzylmethylphenylammonium bromide,[20] and of the formation of urea from ammonium cyanate.[21]

In contrast, the rearrangement of α-phenylallyl alcohol does not, according to the oxotropic mechanism of Braude *et al.*[3], involve the appearance or disappearance of charges. The reaction follows the course:

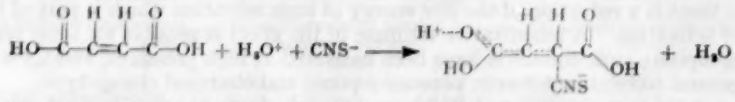


The only changes in solvation will be due to differences in ionic size, so that pressure may be expected not to disturb any of the stages of the reaction appreciably. A correspondingly small effect on the rate is observed, and in aqueous dioxan this is at least partially attributable to the increase of catalyst concentration caused by the volume compression of the solvent, for which no correction was made.

Nozaki and Ogg,[9] in the mechanism they advanced for the potassium thiocyanate-catalysed isomerisation of maleic acid, postulated the addition of a proton to a carbonyl

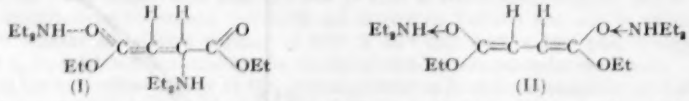
[19] Hughes and Ingold, *Quart. Rev.*, 1952, **6**, 34.
[20] Perrin, *Trans. Faraday Soc.*, 1938, **34**, 144.
[21] David and Hamann, *ibid.*, 1954, **50**, 1188.

oxygen atom of the acid molecule, and the approach of a CNS^- anion to the more remote of the olefinic carbon atoms.



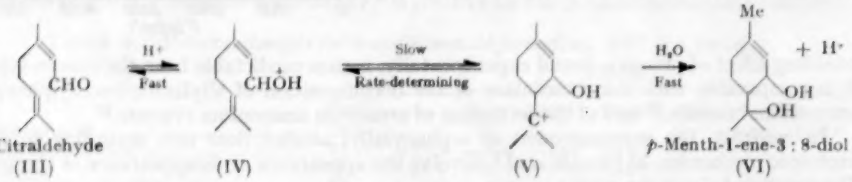
By this process the double bond is sufficiently shifted for isomerisation to occur. The protons are derived from the ionisation of other acid molecules and for this reason the isomerisation should be of indeterminate order, between $1\frac{1}{2}$ and 2, with respect to the maleic acid concentration. As the ionic charges do not change in the transition state, pressure will be expected to accelerate the reaction chiefly by increasing the proton concentration, through further ionisation of the weak acid. The moderate acceleration observed is of the magnitude to be expected from the effect of pressure on the ionic equilibrium of fumaric acid which was measured by Brander.[22]

The other *cis-trans*-isomerisation (of diethyl maleate) was established to be of second



order with respect to the diethylamine catalyst by Nozaki,[6] who confirmed the absence of catalysis by tertiary amines. Nozaki formulates the transition state as (I) in which association of an amine-nitrogen atom with an olefinic carbon atom, and of an amine-hydrogen atom with a carbonyl-oxygen atom, produces an electron shift sufficient to permit isomerisation. The alternative structure (II) appears preferable, but in each the association of amine and ester involves the appearance of whole or partial ionic charges.[23] In accordance with this theory the acceleration by pressure is considerably greater than for the thiocyanate-catalysed isomerisation of the acid, and is of the order of magnitude found for Menschutkin reactions.[20]

The effects of pressure on the four reactions discussed above are all reconcilable with the ionic solvation theory, but this is apparently not the case for the cyclisation of citraldehyde. The mechanism advanced by Price and Dickman [8] is as shown, the rate-



determining step being the isomerisation (IV) $\rightleftharpoons$ (V). There is no disappearance of ionic charge, so that according to the solvation theory pressure should have little effect on the rate, as in the case of α-phenylallyl alcohol. The measurements, however, show a strong accelerating effect, which diminishes fairly rapidly with increasing pressure. The explanation is probably to be found in the special nature of the reaction, and it is possible that at high pressures the entropy of activation associated with the ring-closure is reduced. Unfortunately no conclusions on this point can be drawn from the Arrhenius parameter A since the reacting species from which the transition state is formed is the ion (IV), of unknown concentration, and not the neutral molecule (III).

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[*Received, July 22nd, 1955.*]

[22] Brander, *Soc. Sci. Fennica, Commentationes Phys.-Math.*, 1932, **6**, (8) 1.
[23] Davies and Evans, *Trans. Faraday Soc.*, 1955, **51**, 1506.

201. *Acrylonitrile in Organic Syntheses. Part II.* Conditions for Monocyanoethylation.*

By A. D. Campbell and I. D. R. Stevens.

Conditions are described for the preparation of the monocyanoethylation product of certain compounds containing an active methyl or methylene group by direct cyanoethylation and also by a disproportionation reaction from the di- or tri-cyanoethylation products.

Derivatives of tetrahydropyridine were obtained from δ-keto-nitriles under alkaline conditions.

Acrylonitrile normally causes di- or tri-cyanoethylation of compounds having an active methylene or methyl group and, in general, indirect methods such as the basic hydrolysis of cyanoethylated monoalkylacetoacetic esters [1] are used to afford monocyanoethylation products. We now record some attempts to find conditions which will give predominantly monocyanoethylation in the direct reaction.

Although deoxybenzoin is reported to react with 2 mols. of acrylonitrile in dioxan to give γ-benzoyl-γ-phenylpimelonitrile [2] we find, when using *tert.*-butanol as solvent, that the crystalline monocyanoethylation product, δ-oxo-γδ-diphenylvaleronitrile, frequently crystallises during the reaction. When caused to react in equimolar proportions these reactants give an almost quantitative yield of the mononitrile. Similarly phenylacetone with 1 mol. of acrylonitrile gives 5-oxo-4-phenylhexanonitrile, characterised by hydrolysis to the acid, but in this case monocyanoethylation takes place only if the reaction is carried out at 60—70°. Lower temperatures favour the formation of the crystalline dicyanoethylation product previously prepared by Bruson and Riener.[2] Two closely related compounds, 1-naphthyl- and 3 : 4-methylenedioxyphenyl-acetone, also react with 1 mol. of acrylonitrile in *tert.*-butanol but give lower yields.

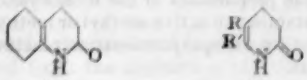
A previous paper [3] described conditions for the monocyanoethylation of phenylacetonitrile by use of an excess of boiling nitrile as solvent. Further investigation shows that monocyanoethylation also takes place in refluxing nitrobenzene but not in tetrachloroethane. The reversibility of the cyanoethylation reaction at high temperatures is illustrated in the formation of α-phenylglutaronitrile by treatment of boiling phenylacetonitrile with its dicyanoethylation product. Although this "reversed" Michael-type reaction gives a good yield of the monocyanoethylation product the latter compound is stable if refluxed with *tert.*-butanol containing Triton B, conditions which favour dicyanoethylation in the normal reaction.

Rogers's method [3] may also be used for the cyanoethylation of ketones. Acetophenone and related compounds readily react with 3 mols. of acrylonitrile [4] but when an excess of boiling acetophenone is treated with acrylonitrile a mixture of δ-oxo-δ-phenylvaleronitrile (by monocyanoethylation) and γ-benzoylpimelonitrile (by dicyanoethylation) is obtained. The same two nitriles, which were hydrolysed to the respective acids,[5] are formed when γ-benzoyl-γ-2-cyanoethylpimelonitrile [2] is treated with excess of acetophenone under similar conditions. The cyanoethylation of *cyclo*hexanone has been investigated by Bruson and Riener,[2] Levina, Shusherina, and Kaminskaya,[6] and more recently by Burnell and Taylor.[7] The last workers show that the yield of dicyanoethylation product is greater if limited quantities of acrylonitrile are used. When Rogers's method is used the product is mainly the monocyanoethylation product together with a smaller quantity of dicyanoethylation product.

* Part I, *J.*, 1954, 1377.

[1] Albertson, *J. Amer. Chem. Soc.*, 1950, **72**, 2594; Misra and Shukla, *J. Indian Chem. Soc.*, 1953, **30**, 37.
[2] Bruson and Riener, *J. Amer. Chem. Soc.*, 1942, **64**, 2850.
[3] Campbell, *J.*, 1954, 1377; cf. Rogers, U.S.P. 2,460,536; *Chem. Abs.*, 1949, **43**, 3446.
[4] Bruson, "Organic Reactions," 1949, Vol. V, p. 101.
[5] Auger, *Ann. Chim. Phys.*, 1891, **22**, 360.
[6] Levina, Shusherina, and Kaminskaya, *Doklady Akad. Nauk. S.S.S.R.*, 1952, **86**, 79.
[7] Burnell and Taylor, *J.*, 1954, 3486.

During preliminary investigations certain δ-oxo-nitriles were found to give isomeric hydro-oxopyridines when refluxed with potassium hydroxide in *tert.*-butanol, the products being similar to those obtained by acid-catalysed rearrangement:[8,9] 2-2′-cyanoethyl-*cyclo*hexanone gave 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-2-oxoquinoline (I) which was readily dehydrogenated to 2-quinolone, and δ-oxo-γδ-diphenylvaleronitrile and 5-oxo-4-phenyl-



(I) (II) (III)

hexanonitrile afforded 1 : 2 : 3 : 4-tetrahydro-2-oxo-5 : 6-diphenylpyridine (II; R = R′ = Ph) and 1 : 2 : 3 : 4-tetrahydro-6-methyl-2-oxo-5-phenylpyridine (II; R = Ph, R′ = Me) respectively which were dehydrogenated to 5 : 6-diphenyl- (III; R = R′ = Ph) and 6-methyl-5-phenyl-2-pyridone (III; R = Ph, R′ = Me). The infrared spectra of the three hydro-oxopyridines showed absorption bands near 3200 and 3070 cm.$^{-1}$ characteristic of the NH stretching frequency of cyclic lactams [10] and at about 1670 cm.$^{-1}$ (broad or double band) due to the carbonyl group. This is in accordance with the structures previously assigned. These isomerisations show that refluxing conditions should be avoided when using potassium hydroxide as the catalyst in the cyanoethylation of ketones in *tert.*-butanol.

Experimental

δ-Oxo-γδ-diphenylvaleronitrile.—Acrylonitrile (6 g.) was added dropwise with stirring to deoxybenzoin (22 g.) and "Triton B" (2 g.) in *tert.*-butanol (50 g.) with cooling to 45—50°. After 3 hours' stirring at 50° the mixture was poured into dilute hydrochloric acid, and the precipitate was filtered off and recrystallised from ethanol, to give the *nitrile* (26 g.), needles, m. p. 86·7—87° (Found: N, 5·7. $C_{17}H_{15}ON$ requires N, 5·6%). Hydrolysis by aqueous potassium hydroxide gave δ-oxo-γδ-diphenylvaleric acid (90%) as needles, m. p. 134—135° (from ethanol) (Knoevenagel [11] gives m. p. 136°). It gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 122—123°, as yellow prisms from ethanol (Found: N, 12·2. $C_{23}H_{20}O_6N_4$ requires N, 12·5%).

5-Oxo-4-phenylhexanonitrile.—Phenylacetone (13 g.) was similarly treated with acrylonitrile (5 g.) with cooling to 60—70°. The oil obtained on acidification of the mixture was taken up in ether and distilled, to give the *nitrile* (12 g.), b. p. 185—190°/18 mm. (Found: N, 7·8. $C_{12}H_{13}ON$ requires N, 7·5%). The residue afforded γ-acetyl-γ-phenylpimelonitrile (2·5 g.), m. p. 110° on recrystallisation from ethanol (charcoal). Bruson and Riener [2] give m. p. 109—110°.

5-Oxo-4-phenylhexanoic Acid.—Acidification of the mixture from the hydrolysis of the above nitrile (36 g.) (6 hr. with boiling aqueous potassium hydroxide) gave the *acid* (36 g.) which was distilled (b. p. 215—220°/18 mm.) and afforded prisms, m. p. 42°, on crystallisation from benzene–light petroleum (Found: C, 70·0; H, 6·8. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). It gave a *semicarbazone*, m. p. 168—168·5° (Found: N, 16·7. $C_{13}H_{17}O_3N_3$ requires N, 16·9%), and an orange 2 : 4-*dinitrophenylhydrazone*, m. p. 116—117° (Found: N, 14·6. $C_{18}H_{18}O_6N_4$ requires N, 14·5%), both as needles from ethanol. Recrystallisation of the acid from water gave the *monohydrate*, m. p. 51—52° (Found: equiv., 220; C, 63·8; H, 6·8. $C_{12}H_{14}O_3,H_2O$ requires equiv., 224; C, 64·3; H, 7·2%). Cyclisation, by hydrogen fluoride, of the acid obtained on Clemmensen reduction of the keto-acid afforded 4-ethyl-1 : 2 : 3 : 4-tetrahydro-1-oxonaphthalene which gave a semicarbazone, m. p. 181·5—182°. Levy [12] gives m. p. 183° (corr.) for the semicarbazone.

4-1′-Naphthyl-5-oxohexanonitrile.—Acrylonitrile (1·5 g.) and 1-naphthylacetone (5 g.), reacting under conditions similar to those described for phenylacetone, gave the *nitrile* (4·2 g.), b. p. 195—200°/6 mm. (Found: N, 5·6. $C_{16}H_{15}ON$ requires N, 5·9%). Hydrolysis with aqueous sodium hydroxide gave 4-1′-*naphthyl-5-oxohexanoic acid*, b. p. 215—220°/6 mm. (Found: C, 75·0; H, 6·0. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%). Plates, m. p. 81—82°, separated from aqueous ethanol on long storage.

4-(3 : 4-Methylenedioxyphenyl)-5-oxohexanonitrile (10·6 g.), b. p. 220—225°/20 mm., was

[8] Allen and Ball, *J. Amer. Chem. Soc.*, 1937, **59**, 686.
[9] Kohler, Graustein, and Merrill, *ibid.*, 1922, **44**, 2536.
[10] Bellamy, "Infra-red Spectra of Complex Molecules," Methuen and Co., London, 1954, p. 179.
[11] Knoevenagel, *Ber.*, 1888, **21**, 1351.
[12] Levy, *Compt. rend.*, 1933, **197**, 772.

similarly prepared from 3 : 4-methylenedioxyphenylacetone (36 g.) and acrylonitrile (10·6 g.) (Found : N, 5·8. $C_{13}H_{13}O_3N$ requires N, 6·1%). It was hydrolysed by aqueous sodium hydroxide to the *acid*, b. p. 240—245°/12 mm. (Found : C, 62·1; H, 5·5. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%), whose *monohydrate* crystallised as needles, m. p. 62—62·5°, from aqueous ethanol (Found : C, 58·1; H, 5·9. $C_{13}H_{14}O_5,H_2O$ requires C, 58·2; H, 6·0%).

α-*Phenylglutaronitrile*—(*a*) A mixture of acrylonitrile (10·6 g.) and phenylacetonitrile (23·4 g.) was added dropwise during 25 min. to a refluxing solution of nitrobenzene containing sodium cyanide (1 c.c. of a 50% aqueous solution). The solution was refluxed for a further 35 min. and then distilled, to give solvent, followed by α-phenylglutaronitrile (12·8 g.), b. p. 197—199°/14 mm. Campbell [3] gives b. p. 200—205°/15 mm.

(*b*) γ-Cyano-γ-phenylpimelonitrile (5 g.), phenylacetonitrile (50 g.), and sodium cyanide (0·2 g. in 0·3 c.c. of water) were heated at 225° for 3 hr. and the resulting solution was distilled, to give unchanged phenylacetonitrile, followed by α-phenylglutaronitrile (6·25 g.), b. p. 189—193°/8 mm.

δ-*Oxo*-δ-*phenylvaleronitrile* and γ-*Benzoylpimelonitrile*.—(*a*) Acrylonitrile (8·1 g.) was added dropwise during 5 min. to a refluxing solution of acetophenone (60 g.) containing sodium cyanide (0·5 g.) and water (0·25 g.). The solution was refluxed a further 30 min. and distilled, to give unchanged acetophenone, followed by two fractions, the first of which afforded δ-oxo-δ-phenylvaleronitrile, b. p. 178—182°/8 mm., on redistillation. Crystallisation from ethanol gave plates of the nitrile (3·2 g.), m. p. 38—39° (Found : C, 76·2; H, 6·1. Calc. for $C_{11}H_{11}ON$: C, 76·3; H, 6·4%); Allen and Ball [4] give m. p. 38°. The second fraction afforded γ-*benzoylpimelonitrile* (3·0 g.), b. p. 203—205°/0·4 mm. (Found : C, 74·3; H, 6·5. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%), which was hydrolysed by refluxing sulphuric acid, acetic acid, and water (1 : 1 : 1) to γ-*benzoylpimelic acid* which crystallised from water as needles, m. p. 110—111° (Found : C, 63·9; H, 5·9. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%).

(*b*) γ-Benzoyl-γ-2-cyanoethylpimelonitrile (10 g.) was refluxed for 3 hr. with acetophenone (50 g.), sodium cyanide (0·25 g.), and water (0·3 g.), and the resulting solution was distilled, to give δ-oxo-δ-phenylvaleronitrile (5·4 g.), b. p. 194—197°/12 mm., m. p. 37—38°, followed by γ-benzoylpimelonitrile (4·5 g.), b. p. 248—256°/12 mm.

2-2′-*Cyanoethylcyclohexanone and* 2 : 2-*Di*-2′-*cyanoethylcyclohexanone*.—A mixture of acrylonitrile (10·6 g.) and *cyclo*hexanone (48 g.) was added dropwise during 30 min. to refluxing *cyclo*hexanone (50 g.) containing sodium cyanide (1 c.c. of a 50% aqueous solution). After refluxing for a further 15 min. the solution was distilled to give *cyclo*hexanone, followed by two fractions. Redistillation of the first fraction gave 2-2′-cyanoethyl*cyclo*hexanone (10·5 g.), b. p. 145—148°/11 mm. (Found : C, 71·3; H, 8·5. Calc. for $C_9H_{13}ON$: C, 71·5; H, 8·7%); Bruson and Riener [2] give b. p. 138—142°/10 mm. The second fraction, 2 : 2-di-2′-cyanoethyl*cyclo*hexanone (3·0 g.), was a pale yellow oil, b. p. 243—250°/11 mm. (Found : C, 70·7; H, 7·4; N, 14·0. Calc. for $C_{13}H_{16}ON_2$: C, 70·6; H, 7·9; N, 13·7%), from which crystals, m. p. 67—68° separated; Bruson and Riener [2] give b. p. 195—198°/1 mm., m. p. 69°, for the dicyanoethylation product.

1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*Octahydro*-2-*oxoquinoline*.—2-2′-Cyanoethyl*cyclo*hexanone (11·5 g.) was refluxed for 4 hr. with methyl-alcoholic potassium hydroxide (3 c.c. of a 30% solution) in *tert.*-butanol (20 c.c.). The semisolid which separated after neutralisation with dilute hydrochloric acid and dilution with water was washed with ether and recrystallised from ethanol, to give colourless needles of the quinoline derivative (3·25 g.), m. p. 143—144° (Found : C, 71·3; H, 8·4. Calc. for $C_9H_{13}ON$: C, 71·5; H, 8·7%). Lions [13] gives m. p. 144°. The infrared spectrum showed max. (among others) at 3175, 3080, and 1670 cm.$^{-1}$. Dehydrogenation at 360° with 30% palladium–charcoal gave pale yellow needles of 2-hydroxyquinoline, m. p. 193—194°.

1 : 2 : 3 : 4-*Tetrahydro*-2-*oxo*-5 : 6-*diphenylpyridine*.—Similarly prepared from δ-oxo-γδ-diphenylvaleronitrile (10 g.), this *pyridine* derivative recrystallised from ethanol as plates (1·25 g.), m. p. 214—214·5° (Found : C, 81·6; H, 5·7; N, 5·8. $C_{17}H_{15}ON$ requires C, 81·9; H, 6·1; N, 5·6%). The infrared spectrum showed max. (among others) at 3200, 3060, and 1666 cm.$^{-1}$. Starting material (6 g.) was recovered. Dehydrogenation with palladium–charcoal afforded 5 : 6-*diphenyl*-2-*pyridone* as pale lemon-yellow needles (from ethanol), m. p. 262·5—263° (Found : C, 82·7; H, 5·6. $C_{17}H_{13}ON$ requires C, 82·6; H, 5·3%).

1 : 2 : 3 : 4-*Tetrahydro*-6-*methyl*-2-*oxo*-5-*phenylpyridine* (3·0 g.), similarly prepared from 5-oxo-4-phenylhexanonitrile (10 g.) (6 hr. at the b. p.), crystallised from ethanol as plates, m. p. 169—170° (Found : C, 76·9; H, 7·4; N, 7·1. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0; N, 7·5%).

[13] Lions, *J. Proc. Roy. Soc. New South Wales*, 1938, **71**, 192.

Included in the infrared spectrum were max. at 3200, 3070, 1650, and 1675 cm.$^{-1}$. An isomeric, unidentified, basic substance, precipitated when the aqueous solution was made alkaline, recrystallised from ethanol as needles (0·5 g.), m. p. 248° (with decomp.) (Found: C, 77·4; H, 6·5; N, 7·7%).

Dehydrogenation of the pyridine derivative afforded *6-methyl-5-phenyl-2-pyridone*, plates m. p. 214—215° (from ethanol) (Found: C, 77·9; H, 5·7. $C_{12}H_{11}ON$ requires C, 77·8; H, 6·0%.

The authors thank Dr. G. Eglinton for infrared determinations and Messrs. C. L. Carter and J. M. L. Cameron, and Miss M. W. Christie for microanalyses.

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202. *Polyfluoroalkyl Compounds of Silicon. Part I. Reaction of Trichlorosilane with Tetrafluoroethylene.**

By R. N. HASZELDINE and R. J. MARKLOW.

The photochemical reaction of trichlorosilane with tetrafluoroethylene yields $H{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}SiCl_3$, where $n = 1$, 2, 3, etc. The reaction can be controlled to give mainly the compound with $n = 1$. Aqueous-alkaline hydrolysis of the silicon compounds yields the series $H{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}H$. The pyrolysis, hydrolysis, methanolysis, and chlorination of certain polyfluoroalkyl silicon compounds are described, and their infrared spectra are presented.

THE thermal and chemical stability of the fluorocarbons and many of their derivatives is now well established. As alkyl-silicon compounds and silicones are also stable thermally and chemically, we thought that a combination of the two types of compound to give polyfluoroalkyl-silicon compounds and polyfluoroalkyl-silicones would be worthy of investigation, since such compounds might show high thermal, and possibly chemical, stability.

Five methods have been found to be of general use for the preparation of polyfluoroalkyl silicon compounds: (*a*) reaction of a silicon tetrahalide with a polyfluoroalkyl Grignard compound, (*b*) reaction of a sodium or lithium polyfluoroalkyl with a silicon tetrahalide, (*c*) reaction of a polyfluoroalkyl bromide or iodide with silicon in presence of a catalyst, usually copper, (*d*) addition of a silicon compound to an unsaturated linkage in a polyfluoro-compound, and (*e*) addition of a polyfluoroalkyl iodide or bromide to an unsaturated linkage in an alkene–silicon compound. A sixth possible general approach can be visualised, namely, replacement of chlorine, bromine, or iodine in a polyhalogenoalkyl-silicon compound by fluorine. The initial results of a study of methods (*a*), (*b*), and (*c*) have already been briefly reported [1] and will be recorded in subsequent Parts of this series. The present Part illustrates method (*d*) by reaction of trichlorosilane with tetrafluoroethylene, and method (*e*) has been reported recently.[2]

Tetrafluoroethylene is a convenient, readily-available olefin whose polymerisation can often be controlled [3] to give short-chain polymers; this often constitutes a relatively easy route to a homologous series of compounds which possess a reactive functional group at one end of the chain. Sommer, Pietrusza, and Whitmore [4] showed that trichlorosilane reacted by addition with unsubstituted olefins. It seemed probable, from what is now known of

* Presented at Amer. Chem. Soc. Meeting, Minneapolis, 1955.

[1] Haszeldine, Amer. Chem. Soc. Meetings, New York, 1951; Atlantic City, 1952; New York, 1954; *Nature*, 1951, **168**, 1028; *Angew. Chem.*, 1954, **66**, 693.
[2] Haszeldine and Marklow, Amer. Chem. Soc. Meeting, Minneapolis, 1955.
[3] See, *e.g.*, Haszeldine, *J.*, 1953, 3761.
[4] Sommer, Pietrusza, and Whitmore, *J. Amer. Chem. Soc.*, 1945, **67**, 188; 1948, **70**, 484.

polyfluoroalkyl radical reactions, that trichlorosilane would react similarly with tetrafluoroethylene by a suitably initiated free-radical reaction :

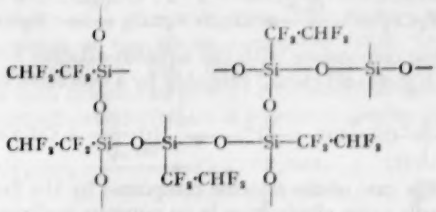
$$SiHCl_3 \longrightarrow SiCl_3\cdot + H\cdot$$
$$SiCl_3\cdot + C_2F_4 \longrightarrow SiCl_3\cdot CF_2\cdot CF_2\cdot \quad \text{(Initiation)}$$
$$SiCl_3\cdot CF_2\cdot CF_2\cdot + C_2F_4 \longrightarrow SiCl_3\cdot CF_2\cdot CF_2\cdot CF_2\cdot CF_2\cdot, \text{ etc.} \quad \text{(Propagation)}$$
$$SiCl_3\cdot[CF_2\cdot CF_2]_n\cdot + SiHCl_3 \longrightarrow SiCl_3\cdot[CF_2\cdot CF_2]_n\cdot H + SiCl_3\cdot \quad \text{(Chain transfer)} \longrightarrow \text{etc.}$$

This has proved to be the case. The Si–H bond appears to be essential for formation of the $SiCl_3$ radical which initiates the reaction, since attempts to use silicon tetrachloride instead of trichlorosilane failed. The failure to achieve homolytic fission of the polar Si–Cl bond by use of heat, light, or peroxide initiators has been noted by previous workers.[4,5] The purely thermal reaction of trichlorosilane with tetrafluoroethylene yields products of the type $H\cdot[CF_2\cdot CF_2]_n\cdot SiCl_3$, but the reaction is not as convenient on a laboratory scale as is a photochemical reaction, since some tetrafluoroethylene is lost by its conversion into perfluoro*cyclo*butane. Photochemical initiation causes a smooth, fast reaction, and light of wavelength > 2200 Å gives an essentially quantitative yield and conversion of tetrafluoroethylene into the compounds $H\cdot[CF_2\cdot CF_2]_n\cdot SiCl_3$. The value of n can be controlled particularly easily in this reaction by the ratio of C_2F_4 to $SiHCl_3$; thus a ratio of 1 : 4 gives the compound with $n = 1$ in *ca.* 60% yield, whereas with a ratio of 1 : 1·2 the yield of the compound with $n = 1$ falls to *ca.* 35% with a 65% yield of products where $n > 1$. Trichlorosilane is thus an efficient chain-transfer reagent, and the speed of reaction shows that the $SiCl_3$ radical is reactive towards tetrafluoroethylene. The absence of even traces of free hydrogen in the reaction products shows that hydrogen-atom combination does not occur, nor does hydrogen formation occur by attack of a hydrogen atom on trichlorosilane to generate the $SiCl_3$ radical. The hydrogen atoms formed initially must thus react with tetrafluoroethylene, but the subsequent stages in the reaction so initiated are similar to those initiated by the $SiCl_3$ radical :

$$SiHCl_3 \longrightarrow SiCl_3\cdot + H\cdot$$
$$H\cdot + CF_2{:}CF_2 \longrightarrow CHF_2\cdot CF_2\cdot \xrightarrow{C_2F_4} CHF_2\cdot[CF_2]_2\cdot CF_2\cdot, \text{ etc.})$$
$$CHF_2\cdot CF_2\cdot + SiHCl_3 \longrightarrow CHF_2\cdot CHF_2 + SiCl_3\cdot$$
$$SiCl_3\cdot + C_2F_4 \longrightarrow SiCl_3\cdot CF_2\cdot CF_2\cdot \xrightarrow{SiHCl_3} SiCl_3\cdot CF_2\cdot CHF_2 + SiCl_2\cdot, \text{ etc.}$$

Small amounts of tetrafluoroethane cannot be detected with the same ease as hydrogen.

Trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane, the compound where $n = 1$, was examined as typical of the series. It reacts rapidly and quantitatively with ice-water to give an ether-soluble polysiloxane $(CHF_2\cdot CF_2\cdot SiO_{1\cdot5})_n$ as a white solid which does not melt below 330°. The polysiloxane is clearly formed by conversion of the $SiCl_3$ group into $Si(OH)_3$, followed by a 3-dimensional condensation to give a product of the type



The polysiloxane is stable to water and aqueous acid, but is decomposed rapidly by cold aqueous sodium hydroxide to liberate 1 : 1 : 2 : 2-tetrafluoroethane and silicate quantitatively. Trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane similarly reacts with cold aqueous alkali to yield 1 : 1 : 2 : 2-tetrafluoroethane and silicate quantitatively. The compounds $CF_2\cdot SiCl_3$ and $(CF_3)_2SiCl_2$ also liberate fluoroform with aqueous alkali though not with

[5] Barry, DePree, Gilbey, and Hook, *J. Amer. Chem. Soc.*, 1947, **69**, 2916.

water.[6] By contrast, trichloro(trichloromethyl)silane is hydrolysed to chloroform and silicate merely by reaction with water at room temperature,[7] so that a polysiloxane cannot be obtained from this compound.

Both members of the series $H{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}SiCl_3$ where $n = 2$ or 3 are hydrolysed by aqueous sodium hydroxide to give quantitative yields of $H{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}H$ ($n = 2$ or 3), and the reaction of trichlorosilane with tetrafluoroethylene followed by hydrolysis in this way constitutes a general method for the preparation of the compounds $H{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}H$, which are otherwise somewhat difficult to obtain. Hydrolysis of the silicon compounds where $n = 2$ or 3 is slower than that of trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane. The increase in the ease of hydrolytic attack

attributed to the increased positive character of silicon when a polyfluoroalkyl group is attached to it is clearly offset to some extent by some other factor in the longer-chain compounds, probably since the polysiloxanes generated initially are only partly soluble in water and are protected by the liberated polyfluorocarbon $H{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}H$ which tends to form a film around the solid polymer. In the latter case, the use of higher temperatures for the hydrolysis might serve to volatilise the polyfluorocarbon.

The marked increase in boiling point on replacement of terminal fluorine atoms in a fluorocarbon by hydrogen is shown below :

Compound	B. p.	Compound	B. p.	Compound	B. p.
$CF_3{\cdot}CF_3$	−79°	$CF_3{\cdot}CHF_2$	−48°	$CHF_2{\cdot}CHF_2$	−20°
$CF_3{\cdot}[CF_2]_2{\cdot}CF_3$	− 5	$CF_3{\cdot}[CF_2]_2{\cdot}CHF_2$	14	$H{\cdot}[CF_2]_4{\cdot}H$	43
$CF_3{\cdot}[CF_2]_4{\cdot}CF_3$	55	$CF_3{\cdot}[CF_2]_4{\cdot}CHF_2$	70	$H{\cdot}[CF_2]_6{\cdot}H$	87

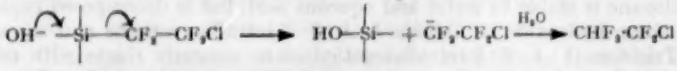
The chlorine atoms in trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane are readily replaced by alkoxy-groups; *e.g.*, the compound $CHF_2{\cdot}CF_2{\cdot}Si(OMe)_3$ was easily prepared by reaction with anhydrous methanol. Aqueous hydrolysis of the trimethoxy-compound gave a polysiloxane very similar to that obtained from the trichloro-compound, and very probably formed from the same intermediate, $CHF_2{\cdot}CF_2{\cdot}Si(OH)_3$; reaction of the trimethoxy-compound or its polysiloxane with aqueous sodium hydroxide again liberated tetrafluoroethane quantitatively.

Trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane is stable at 150° in glass apparatus, and thermal chlorination at this temperature readily yields trichloro-(2-chlorotetrafluoroethyl)-silane. The same compound is obtained almost quantitatively by photochemical chlorination, and fission of the carbon–silicon bond cannot be detected. Aqueous alkaline hydrolysis of the chlorinated material yields 1-chloro-1 : 1 : 2 : 2-tetrafluoroethane quantitatively :

$$CHF_2{\cdot}CF_2{\cdot}SiCl_3 \xrightarrow{Cl_2,\ h\nu} CF_2Cl{\cdot}CF_2{\cdot}SiCl_3 \xrightarrow{OH^-} CF_2Cl{\cdot}CHF_2$$

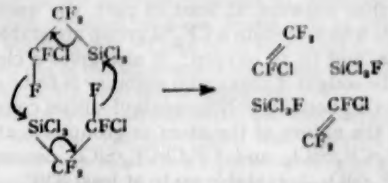
This forms an interesting comparison with the aqueous-alkaline hydrolysis of trichloro-(2-chloroethyl)silane which yields ethylene,[8] probably by a concerted mechanism :

which is prevented in the case of the fluorine compound by the fluorine atoms' stabilising the chlorine atom towards anion elimination in an aqueous medium :

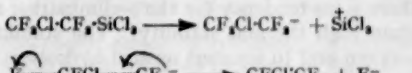


[6] Haszeldine, ref. 1 and later Parts of this series.
[7] Di Giorgio, Sommer, and Whitmore, *J. Amer. Chem. Soc.*, 1948, **70**, 3512.
[8] Sommer, Goldberg, Dorfman, and Whitmore, *ibid.*, 1946, **68**, 1083.

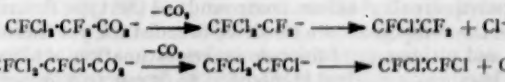
The pyrolysis of trichloro-(2-chloro-1 : 1 : 2 : 2-tetrafluoroethyl)silane was investigated to determine the mode of breakdown of polyfluoroalkyl-silicon compounds. Chlorotrifluoroethylene was the only organic compound obtained at 220°, and this novel reaction is best visualised as a process in which fluoride is transferred to silicon, probably *via* a cyclic intermediate :



The trichlorofluorosilane formed initially could then disproportionate. A mechanism of the type postulated earlier [9] for the formation of polyfluoro-olefins by pyrolysis of alkali-metal salts of polyfluorocarboxylic acids, *i.e.*, halide elimination from a fluoro-carbanion :

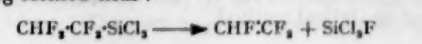


is unlikely, since elimination of chloride rather than of fluoride occurs with polychlorofluoro-acids, *e.g.* :

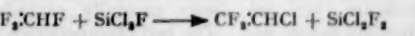


Pyrolysis of the silicon compound resulted exclusively in elimination of fluoride, and tetrafluoroethylene was not a reaction product. A free-radical mechanism following initial homolytic fission of the C–Si bond also seems unlikely, since expulsion of a fluorine atom from $CF_2Cl{\cdot}CF_2{\cdot}$ would be involved.

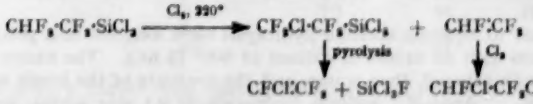
Pyrolysis of trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane at 220° gave approximately equimolar amounts of trifluoroethylene and 1-chloro-2 : 2-difluoroethylene. The first olefin is that expected by analogy with the pyrolysis of trichloro-(2-chloro-1 : 1 : 2 : 2-trifluoroethyl)silane, being formed thus :



but the second olefin was unexpected. Its formation can be attributed to the replacement by chlorine of the lone fluorine atom in trifluoroethylene by reaction with silicon chlorofluorides, *e.g.*,



Thermal chlorination of trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane at temperatures higher than the 150° mentioned earlier gives a mixture of products. At 225°, for example, both chlorination and pyrolysis of the silicon compound occur, to give trichloro-(2-chloro-1 : 1 : 2 : 2-tetrafluoroethyl)silane and trifluoroethylene respectively. The olefin so produced then reacts with chlorine to give 1 : 2-dichlorotrifluoroethane, and the trichloro-(2-chloro-1 : 1 : 2 : 2-tetrafluoroethyl)silane is pyrolysed to give chlorotrifluoroethylene :



The hydrogen chloride liberated during the chlorination reaction does not react with the other products provided that an excess of chlorine is present. Anhydrous hydrogen chloride alone reacts with trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane at 205°, however, to

[9] Haszeldine, *Nature*, 1951, **168**, 1028; *J.*, 1952, 4259; 1954, 4026; 1955, 4291, 4302.

give 1 : 1 : 2 : 2-tetrafluoroethane ($CHF_2{\cdot}CF_2{\cdot}SiCl_3 \longrightarrow CHF_2{\cdot}CHF_2 + SiCl_4$) as well as products formed by pyrolysis of the silicon compound.

The reaction of trichlorosilane with tetrafluoroethylene thus provides a simple and convenient route to polyfluoroalkylsilanes, and the extension of the reaction to other fluoro-olefins will be described later.

The present work thus answers, at least in part, the questions of whether polyfluoroalkyl silicon compounds which contain a $CF_2{\cdot}Si$ group are stable (*a*) to heat, (*b*) to hydrolysis by water, acid, or base, and (*c*) to oxygen; it also gives a clear indication of the types of structure which must be sought if maximum stability is to be obtained in such compounds. The stability of the Si–CF_2 bond in polyfluoroalkyl-silicon compounds clearly depends to an appreciable extent on the nature of the atom or group also attached to the silicon. Thus the compounds $CHF_2{\cdot}CF_2{\cdot}SiCl_3$ and $CF_2Cl{\cdot}CF_2{\cdot}SiCl_3$ decompose at 220°, whereas the polysiloxane $(CHF_2{\cdot}CF_2{\cdot}SiO_{1\cdot5})_n$ is stable up to at least 330°. Chlorine is bonded to silicon in the first type of compound, and the relatively weak $\cdot CF_2{\cdot}Si$–X bond (X = Cl, Br, or I), and particularly the tendency for silicon tetrahalide formation by the β-halogen elimination discussed above, leads to thermal instability. The polysiloxane contains a strong $\cdot CF_2{\cdot}Si$–O· bond and there is no tendency for the β-elimination reaction; such a structure must be sought to attain high thermal stability. The stability of the polyfluoroalkyl-silicon compounds to oxygen and to aqueous or acid hydrolysis is good, and there is little doubt that the stability to alkaline hydrolysis can be improved or made complete by modifying the molecule so that the polyfluoroalkyl group is in a suitable position relative to silicon without loss of the thermal stability found for the $\cdot CF_2{\cdot}Si{\cdot}O\cdot$ system.

The analysis of polyfluoroalkyl-silicon compounds of the type described above presents some problems, since the compounds are sensitive to moisture, yet thermally stable, and the presence of fluorine and ultimately of fluoride makes estimation of silicon by conventional methods difficult. Jewsbury's method,[10] modified to fit our requirements, was found to be most suitable for determination of silicon as silicate. The silicon in the polyfluoroalkyl-silicon compound was obtained as silicate (*a*) by removal of the polyfluoroalkyl group by hydrolysis with aqueous alkali, or (*b*) by fusion of the compound with sodium in a nickel bomb. Method (*b*) introduced fluoride into the silicate solution, but the procedure adopted was satisfactory in both cases. Many polyfluoroalkyl silicon compounds are hydrolysed quantitatively by aqueous alkali, whereby the silicon compound R_FSi– is converted into R_FH and silicate (R_F = polyfluoroalkyl). If R_FH is sufficiently volatile it can be transferred quantitatively to a vacuum-apparatus and measured, and this constitutes a convenient analytical method.

Experimental

Reactions were carried out in sealed Pyrex or silica tubes which were filled by use of a vacuum-apparatus; moisture, air, etc., were carefully excluded. Trichlorosilane was a commercial sample, redistilled before use. The tetrafluoroethylene was spectroscopically pure and was refractionated *in vacuo*. Reaction products were identified by infrared spectroscopy whenever possible.

Analytical Methods.—(a) *Determination of silicon.* The silicon compound (*ca.* 0·2 g.) was weighed in a Polythene container fitted with a tight stopper, which was then opened under 100 ml. of 10% aqueous " AnalaR " sodium hydroxide in a Polythene beaker. After reaction had ceased, the solution was neutralised (phenolphthalein) with 3N-sulphuric acid, and *ca.* 10 g. of " AnalaR " boric acid were added. After being stirred for 5—10 min., the filtered solution was made up to 250 ml.

Compounds resistant to aqueous alkaline hydrolysis were weighed in a gelatin capsule and heated in a nickel bomb with an excess of sodium at 600° (2 hr.). The excess of sodium was removed by reaction with ethanol, then water, and the contents of the bomb were transferred to a platinum crucible. " AnalaR " sodium hydroxide (2 g.) was added, and the mixture digested for 1—2 hr. After transfer to a Polythene beaker, the mixture was treated as before.

An aliquot part of the neutralised solution containing 0·5—1 mg. of silcon was transferred to a 50-ml. standard flask and made up to *ca.* 40 ml. by addition of 4% " AnalaR " boric acid solution

[10] Jewsbury, *Analyst*, 1950, **75**, 256.

(to form a complex with the fluoride) and 2 ml. of 5N-nitric acid. This was followed by 5 ml. of 10% ammonium molybdate solution, and the solution was then made up to 50 ml. with water. The above procedure converts silicate into yellow silicomolybdic acid. The intensity of the yellow colour was next measured by use of a Unicam Ultraviolet Spectrophotometer at a definite wavelength rather than by use of a Spekker intrument with a specific filter as described by Jewsbury. The optical density of the solution obtained as described above was measured, 5 min. after the solution had been prepared, in 1-cm. Pyrex cells at 420 mμ, with water in the reference cell. The slit width was 0·03 mm. There is no maximum in the absorption curve for the silicomolybdic acid, and 420 mμ is the wavelength where the acid absorbs strongly but the reagents' absorption (unlike that at, *e.g.*, 390 mμ) is negligible.

A standard graph of optical density against silicon content was prepared by use of a standard silicate solution (0·1295 g. of SiO_2 per 100 ml.) which was analysed gravimetrically. This solution was diluted four times to give solution *A*, portions of which were put through the routine described above, the resultant optical density being measured. The results are shown in the annexed Table.

Solution *A* (ml.) ...	0	0·5	1·0	1·5	2·02	2·5	3·0	3·5
Si (mg.)	0	0·162	0·324	0·486	0·654	0·810	0·972	1·134
Optical density ...	0	0·140	0·281	0·420	0·586	0·720	0·858	0·995

(b) *Determination of polyfluoroalkyl groups by hydrolysis.* A weighed amount of a volatile polyfluoroalkyl-silicon compound was transferred *in vacuo* to the cold finger of an evacuated 500-ml. bulb fitted with vacuum tap and taper joint. An excess of aqueous alkali was then added to the bulb by filling the taper joint above the tap with the solution and drawing it into the bulb by momentarily opening the tap. After being vigorously shaken, the volatile product (*e.g.*, $CHF_2{\cdot}CHF_2$ from $CHF_2{\cdot}CF_2{\cdot}SiCl_3$) was transferred to an apparatus for the vacuum-manipulation of gases, where its volume and molecular weight were measured. Polyfluoroalkanes with b. p.s up to 100° can be transferred quantitatively in this way. Less volatile polyfluoroalkyl-silicon compounds (*e.g.*, polysiloxanes) were weighed into a fragile tube which was sealed, then inserted into a larger tube (50 ml.) containing aqueous sodium hydroxide. The larger tube was sealed, then the inner tube broken by shaking. When reaction was complete the volatile products were transferred to the vacuum-apparatus in the usual way.

Photochemical Reaction of Trichlorosilane with Tetrafluoroethylene.—Trichlorosilane (15·2 g., 110 mmoles) and tetrafluoroethylene (6·85 g., 68·5 mmoles), shaken and irradiated in a sealed 200-ml. silica tube (24 hr.), gave liquid products, which were distilled through a small column to give (*a*) unchanged trichlorosilane, b. p. 32°, (*b*) ***trichloro*-(1 : 1 : 2 : 2-*tetrafluoroethyl*)*silane*** (7·1 g., 44%), b. p. 84·5—85·0°, n_D^{18} **1·367** (Found : C, 10·3; H, 0·8; Cl, 45·5, 45·2; Si, 11·8, 11·7%; *M*, 236. $C_2HCl_3F_4Si$ requires C, 10·2; H, 0·4; Cl, 45·4; Si, 11·9%; *M*, 235·5), and (*c*) a residue of higher b. p. (4·0 g.). There are no products other than $H{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}SiCl_3$ formed during this reaction.

The trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane was redistilled through a packed column to remove trichlorosilane, and was checked by infrared spectroscopy before analysis. Chlorine and silicon were determined (*a*) by hydrolysis and (*b*) by sodium fusion. The b. p. of the silicon compound measured by use of an isoteniscope is 84·2°.

The above experiment was repeated with variation in reactant ratio. The effect on the yield of trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane is shown in the annexed Table, where $H{\cdot}[CF_2{\cdot}CF_2]_m{\cdot}SiCl_3$ refers to the polymer containing more than two carbon atoms per molecule. In all cases a small amount of solid formed on the walls of the silica tube.

$SiHCl_3$ (mmoles)	C_2F_4 (mmoles)	Mole ratio $SiHCl_3 : C_2F_4$	$CHF_2{\cdot}CF_2{\cdot}SiCl_3$ Wt. (g.)	Yield (%)	$H{\cdot}[CF_2{\cdot}CF_2]_m{\cdot}SiCl_3$ (g.)
82·5	68·5	1·5	5·4	34	4·8
110	,,	2·0	7·1	44	4·0
220	,,	4·0	9·8	58	3·1
275	,,	5·0	10·1	61	3·0

The material of b. p. higher than that of the compound where $m = 1$, which accumulated during several experiments, was combined and distilled under reduced pressure in a nitrogen atmosphere to give (*a*) ***trichloro*-(1 : 1 : 2 : 2 : 3 : 3 : 4 : 4-*octafluorobutyl*)*silane*** (8·35 g.), b. p. 90°/195 mm. (Found : C, 14·2; H, 0·4; Cl, 31·6; Si, 8·3. $C_4HF_8Cl_3Si$ requires C, 14·3; H, 0·3; Cl, 31·8; Si, 8·4%), (*b*) ***trichloro*-(1 : 1 : 2 : 2 : 3 : 3 : 4 : 4 : 5 : 5 : 6 : 6-*dodecafluorohexyl*)*silane*** (4·2 g.), b. p. 128°/205 mm. (Found : C, 16·2; H, 0·4; Cl, 24·7; Si, 6·4. $C_6HF_{12}Cl_3Si$

requires C, 16·5; H, 0·2; Cl, 24·4; Si, 6·4%), and (*c*) a residue (2·0 g.) which set to a paste when cold.

Thermal Reaction of Trichlorosilane with Tetrafluoroethylene.—This was not examined in detail, but experiments showed that at 210° up to 80% of the tetrafluoroethylene was converted into perfluoro*cyclo*butane; the compounds $H{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}SiCl_3$ were also produced and identified by infrared spectroscopy. Further examination of this reaction at temperatures below 200°, with peroxide or azo-compound initiators, would probably enable much better yields of the required silicon compounds to be obtained.

Attempted Reaction of Silicon Tetrachloride with Tetrafluoroethylene.—In a single experiment, silicon tetrachloride (50 mmoles) and tetrafluoroethylene (12·5 mmoles) were heated in presence of benzoyl peroxide (0·83 mmole) at 120° for 16 hr. The product was a thin gel suspended in silicon tetrachloride. Tetrafluoroethylene (40%) and silicon tetrachloride were recovered by distillation, which left a residue of a tetrafluoroethylene polymer and organic matter from the decomposed peroxide. Spectroscopic examination identified the polytetrafluoroethylene, and chemical examination showed that no carbon–silicon bonds were present.

In a single experiment silicon tetrachloride (42·5 mmoles) and tetrafluoroethylene (14·8 mmoles), heated at 230° (15 hr.) in a 20-ml. autoclave, gave only unchanged silicon tetrachloride, perfluoro*cyclo*butane, and polytetrafluoroethylene. Polyfluoroalkyl-silicon compounds were not produced.

Alkaline Hydrolysis of Compounds $H{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}SiCl_3$.—(a) *Trichloro-*(1 : 1 : 2 : 2-*tetrafluoroethyl*)*silane.* The silicon compound (0·456 g., 1·94 mmoles), shaken with 10% aqueous sodium hydroxide (20 ml.) for 5 min., gave, on fractionation *in vacuo*, 1 : 1 : 2 : 2-tetrafluoroethane (1·92 mmoles, 99·2%), b. p. (isoteniscope) −20° (Found : C, 23·4; H, 2·1%; *M*, 103. Calc. for $C_2H_2F_4$: C, 23·5; H, 2·0%; *M*, 102). Henne and Renoll [11] report b. p. −23°. A similar experiment using 2% aqueous sodium hydroxide gave a 99·3% yield of tetrafluoroethane from trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (0·323 g., 1·37 mmoles).

(b) *Trichloro-*(1 : 1 : 2 : 2 : 3 : 3 : 4 : 4-*octafluorobutyl*)*silane.* This compound appeared to react only slowly with aqueous alkali at room temperature. A sample (1·104 g., 3·0 mmoles) was sealed with 10% aqueous sodium hydroxide (10 ml.) and heated at 100° (4 hr.). Fractionation of the volatile products *in vacuo* followed by distillation at atmospheric pressure through a short column, gave 1 : 1 : 2 : 2 : 3 : 3 : 4 : 4-*octafluorobutane* (3·0 mmoles, 100%), b. p. (isoteniscope) 43° (Found : C, 23·8; H, 1·0%; *M*, 201. $C_4H_2F_8$ requires C, 23·8; H, 1·0%; *M*, 202).

(c) *Trichloro-*(1 : 1 : 2 : 2 : 3 : 3 : 4 : 4 : 5 : 5 : 6 : 6-*dodecafluorohexyl*)*silane.* The compound appeared to be incompletely hydrolysed under the conditions used for (a) above. A sample (1·028 g., 2·35 mmoles) and 10% aqueous sodium hydroxide (10 ml.), heated at 100° (7 hr.), gave, on fractionation of the volatile products *in vacuo*, followed by distillation at atmospheric pressure through a short column, 1 : 1 : 2 : 2 : 3 : 3 : 4 : 4 : 5 : 5 : 6 : 6-*dodecafluorohexane* (2·35 mmoles, 100%), b. p. (isoteniscope) 87° (Found : C, 23·6; H, 1·1%; *M*, 303. $C_6H_2F_{12}$ requires C, 23·8; H, 0·7%; *M*, 302).

Aqueous Hydrolysis of Trichloro-(1 : 1 : 2 : 2-*tetrafluoroethyl*)*silane.*—Reaction of the silane (0·266 g., 1·125 mmoles) with water (20 ml.) was immediate but gave no volatile products. An aqueous solution containing a fine suspension was obtained after 5 minutes' shaking. Addition of 10% aqueous sodium hydroxide (10 ml.) brought about immediate evolution of 1 : 1 : 2 : 2-tetrafluoroethane (1·12 mmoles, 99·7%).

Trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (1·631 g.) was dissolved in anhydrous ether (100 ml.) then shaken (5 min.) with ice water (50 ml.). The ether layer and subsequent ethereal extracts (3 × 25 ml.) of the aqueous solution were combined. Evaporation of the ether gave a viscous oil, which when dried *in vacuo* (P_2O_5) yielded a brittle glass. This was treated with light petroleum (b. p. 60—80°) to remove traces of occluded organic matter. The residual material was a white solid *polysiloxane* of formula $[CHF_2{\cdot}CF_2{\cdot}SiO_{1\cdot5}]_n$, (0·914 g., 92%) [Found : C, 15·9; H, 1·1; Si, 18·0. $(C_2HO_{1\cdot5}F_4Si)_3$ requires C, 15·6; H, 0·7; Si, 18·3%]. The polysiloxane was insoluble in water, benzene, carbon tetrachloride, and light petroleum, moderately soluble in acetone or ethanol, and readily soluble in ether. It did not melt below 330°.

Reaction of the polysiloxane (0·078 g.) with 10% aqueous sodium hydroxide (20 ml.) was rapid and yielded (5 min.) 1 : 1 : 2 : 2-tetrafluoroethane (0·52 g., 100%).

Trimethoxy-(1 : 1 : 2 : 2-*tetrafluoroethyl*)*silane.*—Trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (3·103 g., 13·2 mmoles) was frozen in a tube with dry methanol (1·265 g., 39·6 mmoles) and a

[11] Henne and Renoll, *J. Amer. Chem. Soc.*, 1936, **58**, 887.

reflux condenser was attached to the tube. Reaction occurred as the tube warmed to room temperature, and evolution of hydrogen chloride was complete after the reactants had been heated on a water-bath (15 min.). The product was transferred to a distillation apparatus, and dry nitrogen was bubbled through the liquid for 1 hr. to remove hydrogen chloride. Distillation then gave only *trimethoxy*-(1 : 1 : 2 : 2-*tetrafluoroethyl*)*silane* (2·15 g., 74%), b. p. 98°/190 mm. (Found : C, 26·9; H, 4·2; Si, 12·6. $C_5H_{10}O_3F_4Si$ requires C, 27·0; H, 4·5; Si, 12·6%).

Reaction of the chloro-compound with the equivalent amount of methanol gives better results than use of an excess of methanol, which appears to form an azeotrope with the required product, and readily absorbs the hydrogen chloride liberated during the reaction.

Trimethoxy-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (0·0762 g.) reacted with 10% aqueous sodium hydroxide (20 ml.) at room temperature to give 1 : 1 : 2 : 2-tetrafluoroethane (0·0349 g., 99·7%).

The trimethoxy-compound (0·710 g.) and water (0·4 ml.) were shaken at 0° to give a homogeneous solution (3 min.) which was kept at 0° for 1 hr. The aqueous methanol was removed *in vacuo* to give a white solid polysiloxane (0·458 g., 94%) of formula $(CHF_2{\cdot}CF_2{\cdot}SiO_{1\cdot5})_n$, spectroscopically identical with the product described earlier. It showed similar characteristics when heated.

Trichloro-(2-*chloro*-1 : 1 : 2 : 2-*tetrafluoroethyl*)*silane*.—(a) *Photochemical chlorination.* Trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (3·30 g., 14·0 mmoles) and chlorine (1·056 g., 14·8 mmoles), exposed to ultraviolet light in a silica tube (15 hr.), gave hydrogen chloride (Found : *M*, 37. Calc. for HCl : *M*, 36·5) and *trichloro*-(2-*chloro*-1 : 1 : 2 : 2-*tetrafluoroethyl*)*silane* (2·83 g., 75%), b. p. 102° (Found : C, 9·1; Cl, 39·9; Si, 10·2. $C_2Cl_4F_4Si$ requires C, 8·9; Cl, 39·5; Si, 10·4%).

(b) *Thermal chlorination.* Trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (1·493 g., 6·3 mmoles) and chlorine (0·453 g., 6·4 mmoles) failed to react in a 50-ml. sealed tube heated at 100° or 125°, but the yellow colour began to fade at 150°. After 15 hr. at this temperature, distillation gave hydrogen chloride (5·5 mmoles) (Found : *M*, 36·5) and a liquid (1·4 g.) of higher b. p. which when redistilled yielded trichloro-(2-chloro-1 : 1 : 2 : 2-tetrafluoroethyl)silane (1·0 g., 59%), b. p. 102°. The yield based on the crude liquid is 83%.

Thermal chlorination at higher temperatures yielded more complex products. Trichloro-(1 : 1 : 2 : 2-tetrafluoroethyl)silane (0·89 g., 3·75 mmoles) and chlorine (0·288 g., 4·05 mmoles) gave mainly volatile products when heated in a 50-ml. tube at 225° (18 hr.). Fractionation *in vacuo*, followed by infrared spectroscopic examination and molecular-weight determinations on the fractions obtained, revealed the presence of chlorotrifluoroethylene, a chlorofluoroethane, and unidentified silicon compounds (not the tetrachloride or tetrafluoride). The silicon compounds were removed by reaction with water, and the olefin by reaction with chlorine. Redistillation of the chlorinated product and of the residual material, followed by spectroscopic analysis and molecular-weight determinations, showed that the original reaction had produced chlorotrifluoroethylene (2·35 mmoles, 63%) and 1 : 2-dichlorotrifluoroethane (1·85 mmoles, 49%). Small amounts of an unidentified olefin were also present.

Trichloro-(2-chloro-1 : 1 : 2 : 2-tetrafluoroethyl)silane (0·0941 g.) and 10% aqueous sodium hydroxide (20 ml.), shaken at room temperature (5 min.), gave 1-chlorotetrafluoroethane (0·0470 g., 99·5%), identified by infrared spectroscopy.

Pyrolysis of Trichloro-(2-*chloro*-1 : 1 : 2 : 2-*tetrafluoroethyl*)*silane*.—The compound (0·684 g., 2·51 mmoles), heated at 220° (15 hr.) in a 50-ml. Pyrex tube, gave chlorotrifluoroethylene (2·25 mmoles, 90%), identified spectroscopically. The silicon compounds produced are probably $SiCl_3F$, $SiCl_2F_2$, and SiF_3Cl, since spectroscopic examination showed that neither silicon tetrachloride nor the tetrafluoride was present in any quantity.

Pyrolysis of Trichloro-(1 : 1 : 2 : 2-*tetrafluoroethyl*)*silane*.—The compound (1·014 g., 4·25 mmoles), heated at 220° (15 hr.) in a 50-ml. Pyrex tube, gave trifluoroethylene (1·45 mmoles, 34%) and 1-chloro-2 : 2-difluoroethylene (2·05 mmoles, 49%), fractionated *in vacuo* and identified by infrared spectroscopy.

Reaction of Hydrogen Chloride with Trichloro-(1 : 1 : 2 : 2-*tetrafluoroethyl*)*silane*.—The silicon compound (1·149 g., 4·85 mmoles) and anhydrous hydrogen chloride (6·1 mmoles) failed to react in a sealed 50-ml. Pyrex tube at 185° (15 hr.). Reaction occurred at 205° (15 hr.) to give 1 : 1 : 2 : 2-tetrafluoroethane and 1-chloro-2 : 2-difluoroethylene (identified by infrared spectroscopy) as the main organic products. The silicon tetrahalides produced were removed by reaction with 10% aqueous sodium hydroxide, and reaction of the residual volatile products with chlorine removed the olefin present. Fractionation *in vacuo* and infrared spectroscopic examination showed the residual material to be 1 : 1 : 2 : 2-tetrafluoroethane (1·6 mmoles, 33%).

Infrared Spectra.—The infrared spectra of the following compounds obtained during the present work have been deposited with the Chemical Society:

Compound	C.S. No.	Compound	C.S. No.	Compound	C.S. No.
$SiCl_4$	305	$H{\cdot}[CF_2]_6{\cdot}SiCl_3$	309	$H{\cdot}[CF_2]_6{\cdot}H$	312
$SiHCl_3$	306	$CHF_2{\cdot}CHF_2$	310	$CHF_2{\cdot}CF_2{\cdot}Si(OMe)_3$	313
$CHF_2{\cdot}CF_2{\cdot}SiCl_3$	307	$H{\cdot}[CF_2]_4{\cdot}H$	311	$CF_2Cl{\cdot}CF_2{\cdot}SiCl_3$	314
$H{\cdot}[CF_2]_4{\cdot}SiCl_3$	308				

The Si–H stretching vibration in trichlorosilane is at 4·42, 4·45 μ (doublet) and the appreciable shift to shorter wavelength compared with the corresponding vibration in alkylsilanes (4·7—4·8 μ) is attributed to the inductive effect of chlorine. The C–H stretching vibration in compounds which contain the CHF_2 group is at 3·34 μ and appears as a single sharp band; the C–H deformation vibration appears as a sharp band in the 7·1—7·4 μ region. Both these bands are absent from the spectrum of trichloro-(2-chloro-1 : 1 : 2 : 2-tetrafluoroethyl)silane. The spectrum of the polysiloxane $(CHF_2{\cdot}CF_2{\cdot}SiO_{1\cdot5})_n$ shows the C–H stretching vibration at 3·38 μ. The C–F stretching vibrations appear, as usual, as strong bands in the 8·3—9·1 μ region, and are dwarfed only by the Si–O vibration at 9·10 μ in trimethoxy-(1 : 1 : 2 : 2-tetrafluoroethyl)silane; the last compound shows C–F absorption at 8·37 μ, C–H stretching vibrations at 3·40, 3·52 μ (doublet), and deformation vibrations at 6·85, 7·23 μ. The spectra of the compounds $H{\cdot}[CF_2]_n{\cdot}H$, where $n = 4$ or 6, are sufficiently different to be used diagnostically.

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203. *The Disulphones derived by Oxidation of the Diethyl Dithioacetals of* D-*Galactose,* D-*Mannose, and* D-*Glucose with Peroxypropionic Acid, and their Conversion into Aldopentoses.*[1]

By L. Hough and T. J. Taylor.

Oxidation of D-galactose and D-glucose diethyl dithioacetals with aqueous peroxypropionic acid at room temperature yielded, respectively, D-*talo*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (diethylsulphonyl-α-D-lyxopyranosylmethane) (IV; R = H) and the corresponding D-*manno*-compound (X; R = H). In a similar oxidation of D-mannose diethyl dithioacetal, two compounds were isolated, namely, 1 : 1-diethylsulphonyl-D-*manno*-2 : 3 : 4 : 5 : 6-pentahydroxyhexane (XIII; R = H) and D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (X; R = H) which was identical with that prepared from D-glucose diethyl dithioacetal. Each disulphone was cleaved by dilute aqueous ammonia to give, in high yield, an aldopentose and diethylsulphonylmethane. The periodate oxidation of these disulphones is discussed.

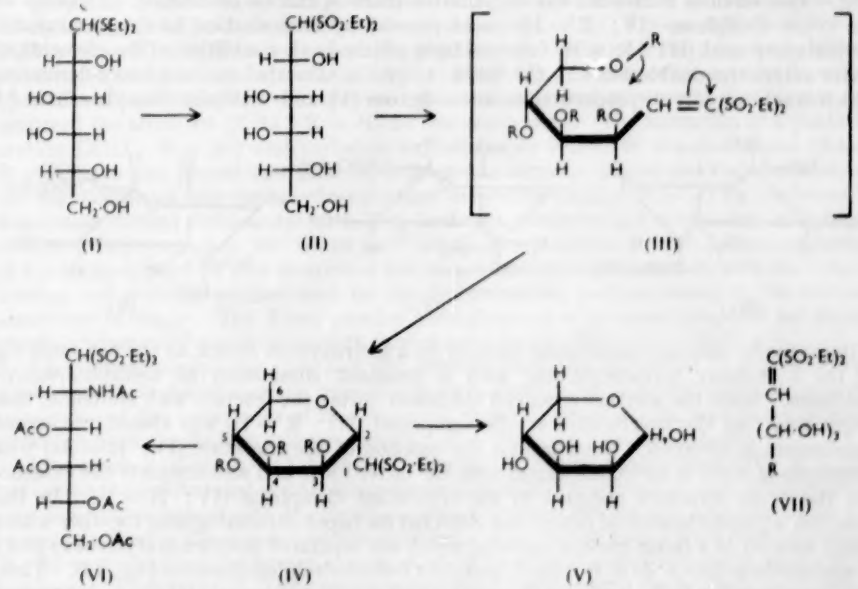
Oxidation of D-aldopentose diethyl dithioacetals with aqueous peroxypropionic acid at room temperature has afforded only unsaturated acyclic disulphones, namely, 1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxypent-1-enes[2] (*e.g.*, VII; R = H). Similar oxidation of L-rhamnose diethyl dithioacetal gave 1 : 1-diethylsulphonyl-L-*arabo*-3 : 4 : 5-trihydroxyhex-1-ene (VII; R = Me) and, in addition, predominantly 1 : 1-diethylsulphonyl-L-*manno*-2 : 3 : 4 : 5-tetrahydroxyhexane.[3] The unsaturated acyclic disulphones are analogous to those obtained when fully acetylated aldohexose diethyl dithioacetals are oxidised with monoperoxyphthalic acid in ether.[4] In contrast, oxidations of D-galactose, D-glucose, and D-mannose diethyl dithioacetals with aqueous peroxypropionic acid at room temperature have given cyclic disulphones and not, as expected, the isomeric unsaturated acyclic

[1] For preliminary communications see Hough and Taylor, *Chem. and Ind.*, 1954, (*a*) 575, (*b*) 1018.
[2] *Idem, J.*, 1955, 1212.
[3] *Idem, J.*, 1955, 3544.
[4] McDonald and Fischer, *J. Amer. Chem. Soc.*, 1952, **74**, 2087.

compounds although the latter are probably formed in the reaction as precursors of the cyclic modifications.

Oxidation of D-galactose diethyl dithioacetal (I) with aqueous peroxypropionic acid at room temperature yielded on concentration of the reaction mixture a highly crystalline disulphone. Although this product gave correct analyses for the expected acyclic tetrahydroxyhex-1-ene (III; R = H), it gave only a pale yellow colour in dry pyridine, even after 24 hours, whereas compounds containing the 1 : 1-diethylsulphonylalk-1-ene grouping show a typical magenta or cherry-red coloration.[2,3] Unlike the mildly acidic, unsaturated acyclic disulphones, derived from D-xylose and L-rhamnose diethyl dithioacetals,[2,3] this compound (IV; R = H) was neutral in aqueous solution and could not be hydrogenated in the presence of Raney nickel. Further, acetylation of the crystalline disulphone by a variety of methods gave only a triacetate (IV; R = Ac) and not D-*lyxo*-3 : 4 : 5 : 6-tetra-*O*-acetyl-1 : 1-diethylsulphonyl-hex-1-ene (III; R = Ac) which was prepared by McDonald and Fischer[4] by oxidising penta-*O*-acetyl-D-galactose diethyl dithioacetal with monoperoxyphthalic acid. Similarly, benzoylation gave only a tribenzoate (IV; R = Bz). It is noteworthy that 1 : 1-diethylsulphonyl-L-*arabo*-3 : 4 : 5-trihydroxyhex-1-ene (VII; R = Me) can be fully acetylated.

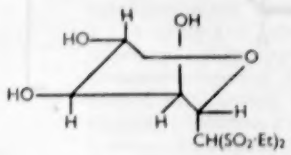
The inability to form a dihydro-derivative and lack of acidity and of coloration with dry pyridine suggest that there is no unsaturated linkage within the molecule, whilst the formation of only tri-*O*-substituted derivatives suggests that the product is cyclic as the result of engagement of a hydroxyl group in the probable intermediate (III; R = H) in intramolecular bonding. The observations that L-rhamnose and aldopentose diethyl dithioacetals afforded unsaturated disulphones, and not cyclic derivatives, on oxidation clearly indicate that the 6-hydroxyl group of the intermediate (III; R = H) is involved in ring closure. Examination of a molecular model (Catalin Ltd.) of the unsaturated



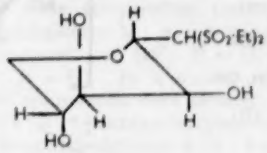
acyclic disulphone (III) showed that the formation of a 2 : 6-epoxy (pyranosyl) ring was possible by attack of the cationoid $C_{(2)}$ on the terminal primary hydroxyl group, thus giving the cyclic disulphone (IV; R = H). Similarly, molecular models of the hex-1-ene derivative (VII; R = Me) and the pent-1-ene derivatives (*e.g.*, VII; R = H) revealed

that owing to restricted rotation about the $C_{(2)}$–$C_{(3)}$ bond the hydroxylated carbon chains were too short to allow ring closure in this way to give the 2 : 5-epoxy (furanosyl) ring. Periodate oxidation gave further evidence in favour of a pyranosyl structure (IV; R = H) for this disulphone (see below). Application of Hudson's isorotation rules to the cyclic disulphone (IV; R = H) ($[M]_D$ + 6308°) and its tri-*O*-acetyl derivative ($[M]_D$ − 10,030°) considered as D-lyxopyranosyl derivatives, and with methyl α- and β-D-lyxopyranoside and their triacetates used to determine values of *B* (−5730° and −11,520° respectively), gave positive values for *A* (+12,038° and +1490° respectively), suggesting an α-configuration for the diethylsulphonylmethyl group. The large difference in the molecular rotations of the cyclic disulphones (IV; R = H and Ac) is perhaps attributable to interaction of one or both of the sulphonyl groups with the neighbouring acetyl groups. This behaviour parallels that of *o*-nitrophenyl β-D-glucoside which has $[M]_D$ −26,500° whereas the tetra-*O*-acetyl derivative [5] has $[M]_D$ + 21,100°. Conformational analysis of D-lyxopyranoside leads to the prediction that it can exist in either the C1 or 1C conformation [6] but that, if D-*talo*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (diethylsulphonyl-α-D-lyxopyranosylmethane) had the C1 conformation (IV*a*), there would be a bulky group in the axial position at the anomeric carbon atom : if, in this conformation the diethylsulphonylmethyl group were in the β-position, there would be a Δ2 condition. Thus the 1C conformation (IV*b*) is preferred since the bulky diethylsulphonylmethyl group is equatorial and there are only two hydroxyl groups in axial positions.

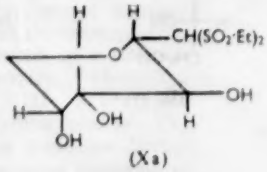
The cyclic disulphone (IV; R = H) was cleaved by an excess of dilute aqueous ammonia (pH 10—11) to give D-lyxose (V) in high yield and diethylsulphonylmethane. The rate of reaction was much slower (6—7 days) than with 1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxypent-1-enes (*e.g.*, VII; R = H) and the orange-red colour which developed in the latter reaction was not encountered.[3,8] This slower rate is probably due to a diminution of cationoid activity at $C_{(2)}$ as the result of theformation of the 2 : 6-epoxy (pyranosyl) ring. Two obvious routes for the degradative reaction can be considered. Cleavage of the cyclic disulphone (IV; R = H) could proceed by isomerisation to the unsaturated acyclic compound (III; R = H) followed by a relatively slow addition of the elements of water across the double bond in the latter, to give a saturated pentahydroxy-derivative which would rapidly disproportionate into D-lyxose (V) and diethylsulphonylmethane.[3,7]



(IVa)



(IVb)



(Xa)

Alternatively, cleavage could occur directly by a hydroxyl-ion attack at the cationoid $C_{(2)}$ of the 2 : 6-epoxy (pyranosyl) ring with a resultant elimination of diethylsulphonylmethane. Since the solution remained colourless during the reaction with ammonia, thus suggesting that the unsaturated acyclic compound (III; R = H) was absent, the second mechanism is favoured. Furthermore, the reaction of the triacetate (IV; R = Ac) with ammonia (*d* 0·88) in methanol agrees with the latter route and also supports the evidence for the cyclic structure assigned to the crystalline disulphone (IV; R = H). In this reaction a preponderance of lyxose was detected on paper chromatograms together with a small amount of a faster-moving material which was separated and then acetylated to give a 2-acetamido-D-*lyxo*-3 : 4 : 5 : 6-tetra-*O*-acetyl-1 : 1-diethylsulphonylhexane (*e.g.*, VI). There can have been but little, if any, of the unsaturated acyclic compound (III; R = Ac) present in this reaction mixture as this would be expected to give in high yield the 2-acetamido-derivative by the addition of the elements of ammonia across the double bond, followed by

[5] Pigman, *J. Res. Nat. Bur. Stand.*, 1944, **33**, 129.
[6] Reeves, *Adv. Carbohydrate Chem.*, 1951, **6**, 107.
[7] Bourne and Stephens, *J.*, 1954, 4009.

an *O*- to *N*-acyl migration, which would prevent subsequent disproportionation of the molecule.[2,4,7] Thus the 2-acetamido-compound (VI) probably originated from a direct nucleophilic attack by ammonia at $C_{(2)}$ of the cyclic disulphone with inversion of configuration at this carbon atom and concurrent fission of the ring. If an *O*- to *N*-acyl migration ensued, the stable 2-acetamido-compound would result, whereas in the absence of such a migration the 2-amino-intermediate would be expected to disproportionate into D-lyxose and diethylsulphonylmethane. Consequently, slow amination relative to deacetylation would lead to a high yield of D-lyxose. Alternatively, lyxose could arise by direct reaction with hydroxyl ions as described above.

Zinner and Falk [8] have prepared 1 : 1-diethylsulphonyl-D-*galacto*-2 : 3 : 4 : 5 : 6-pentahydroxyhexane (II) from D-galactose diethyl dithioacetal using 30% hydrogen peroxide and ammonium molybdate at 0° for oxidation, but these workers have not reported the isolation of the cyclic disulphone (IV; R = H). In our hands, attempted recrystallisation from aqueous ethanol of the D-*galacto*-compound (II) prepared by this method resulted in complete conversion into the cyclic compound (IV; R = H), thus suggesting that it (II) is the primary intermediate in the formation of this derivative. 1 : 1-Diethylsulphonyl-D-*galacto*-2 : 3 : 4 : 5 : 6-pentahydroxyhexane (II) was extremely sensitive to mild alkali. On paper chromatograms, with butan-1-ol–pyridine–water as mobile phase, instantaneous cleavage occurred and only lyxose could be detected. Details of the preparation of 1 : 1-di-*n*-butylsulphonyl-D-*lyxo*-3 : 4 : 5 : 6-tetrahydroxyhex-1-ene and the corresponding di*iso*butylsulphonyl compound have also been reported [8] but, as no proof of the structure was given, a cyclic modification of these compounds must be considered.

D-Glucose diethyl dithioacetal (VIII) was also oxidised with aqueous peroxypropionic acid at room temperature, giving a syrup (A) which has been shown to be D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (diethylsulphonyl-α-D-arabopyranosylmethane) (X; R = H) (see below).

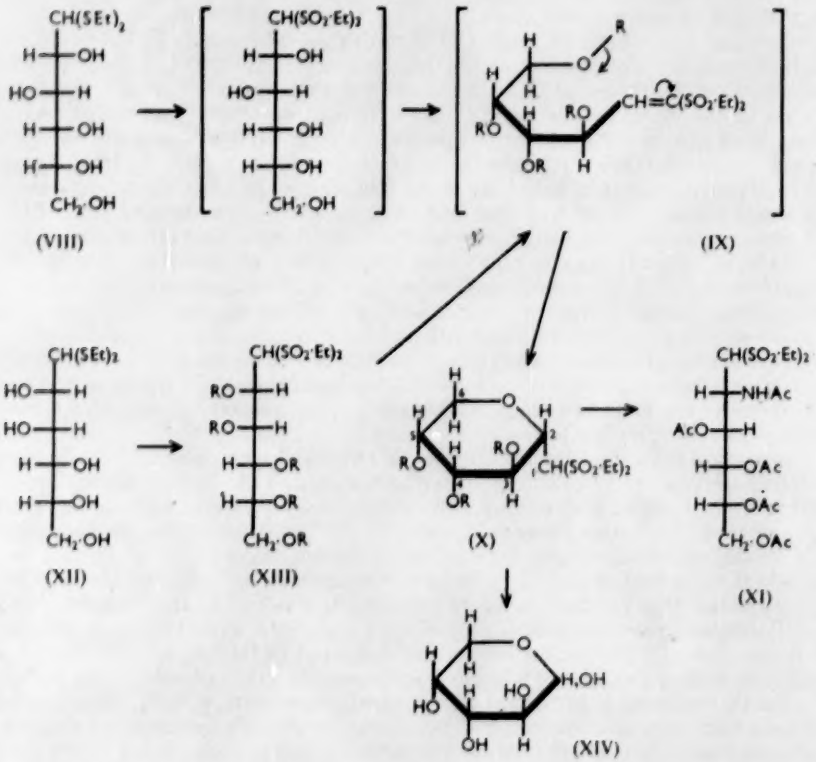
Oxidation of D-mannose diethyl dithioacetal (XII) under the same conditions gave two disulphones, crystalline 1 : 1-diethylsulphonyl-D-*manno*-2 : 3 : 4 : 5 : 6-pentahydroxyhexane (XIII; R = H) (58%) and a syrup (B) identified as D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (X; R = H) (38%). This reaction was first described by McDonald and Fischer,[9] who obtained an uncharacterised mixture of disulphones and proposed the structure (XIII; R = H) for one component. The formation of a penta-*O*-acetate (XIII; R = Ac) and periodate oxidation (see below) of the disulphone (XIII; R = H) have now proved that their supposition was correct. Zinner and Falk [8] also report the preparation of this pentahydroxyhexane derivative (XIII; R = H) by oxidation of D-mannose diethyl dithioacetal with 30% hydrogen peroxide and ammonium molybdate at 0°, but they quote m. p. 167° whilst we [1b] originally reported m. p. 119°. Re-examination of the melting point of this compound has shown considerable variation with the rate of heating and with the method used for the determination, perhaps owing to the extreme sensitivity to alkali. The *X*-ray powder photograph of a specimen prepared by Zinner and Falk's method [8] was identical with that of our material (XIII; R = H).

The syrupy disulphones, (A) and (B), derived from the oxidations of D-glucose and D-mannose diethyl dithioacetals respectively were identical as they had the same specific rotations and the same rates of movement on paper chromatograms, and *X*-ray powder photographs of the derived tribenzoates (X; R = Bz) were indistinguishable.

Like D-*talo*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (IV; R = H), but unlike the unsaturated acyclic disulphones (*e.g.*, VII), the syrups (A) and (B) gave only very pale yellow colours with dry pyridine even after prolonged storage, and they could not be hydrogenated in the presence of Raney nickel. Acetylation gave a crystalline triacetate (X; R = Ac) and not the known D-*arabo*-3 : 4 : 5 : 6-tetra-*O*-acetyl-1 : 1-diethylsulphonylhex-1-ene (IX; R = Ac).[4] This evidence considered together with the fact that L-rhamnose and pentose diethyl dithioacetals do not yield cyclic disulphones suggests that the syrups (A) and (B) are D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-2 : 4 : 5-trihydroxyhexane (X; R = H). Assignment of the D-*manno*-2 : 6-epoxy (α-D-arabopyranosyl) configuration follows from

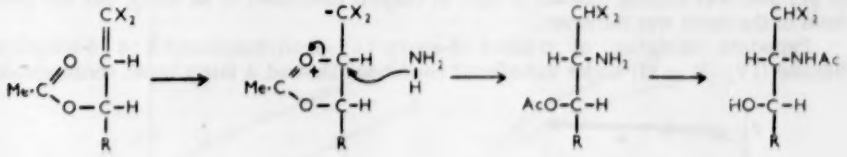
[8] Zinner and Falk, *Chem. Ber.*, 1955, **88**, 566.
[9] McDonald and Fischer, *Biochim. Biophys. Acta*, 1953, **12**, 503.

the application of Hudson's rules of isorotation to the cyclic disulphone (X; R = H) ($[M]_D$ +2092°), with methyl α- and β-D-arabopyranosides ($[M]_D$ −2840°, −40,300° respectively) to determine the value of *B* (−21,570°), thus giving a positive value for *A* (+23,662°). Conformational analysis is in agreement with this configuration, as the pyranosyl modification in the 1C chair form (X*a*) with the bulky diethylsulphonylmethyl group in the equatorial position would be predicted to be the most stable stereoisomer.



Reaction of the triacetate (X; R = Ac) with ammonia (*d* 0·88) in methanol was analogous to the behaviour of the triacetate (IV; R = Ac), already mentioned. Paper chromatography indicated the presence of largely arabinose together with a small amount of faster-moving material which was isolated and then acetylated to give the known D-*gluco*-2-acetamido-3 : 4 : 5 : 6-tetra-*O*-acetyl-1 : 1-diethylsulphonylhexane (XI).[4] This product (XI) would be expected from a nucleophilic attack by ammonia at $C_{(2)}$ of the triacetate (X; R = Ac) with inversion and simultaneous opening of the α-D-arabopyranosyl ring, whereas the β-isomer would lead to the formation of the corresponding D-*manno*-2-2-acetamido-derivative. By the same reasoning, the aforementioned 2-acetamido-3 : 4 : 5 : 6-tetra-*O*-acetyl-1 : 1-diethylsulphonylhexane (VI) is predicted to have the D-*galacto*-configuration. MacDonald and Fischer[4] observed that the acyclic D-*arabo*-3 : 4 : 5 : 6-tetra-*O*-acetyl-1 : 1-diethylsulphonylhex-1-ene (IX; R = Ac) reacted stereospecifically with ammonia to give a product which on acetylation afforded only the D-*gluco*-2-acetamido-derivative (XI). Such stereospecificity would be the consequence of participation of the neighbouring 3-acetoxy-group with the formation of a cyclic ion which could react with ammonia as indicated on p. 975 to give only the D-*gluco*-configuration. In the

case of the cyclic disulphones (IV; X; R = Ac), such a process is considered to be unlikely for the reasons previously mentioned. Reaction of D-*threo*-3 : 4 : 5-tri-*O*-acetyl-1 : 1-diethylsulphonylpent-1-ene with ammonia resembled that of the above tetra-*O*-acetylhex-1-enes (III; IX; R = Ac) and led to the isolation,[2] in high yield, of a crystalline 2-acetamido-compound to which the D-*xylo*-configuration is tentatively assigned from consideration of the neighbouring group participation theory.



(X = SO_2Et)

The syrupy disulphone (X; R = H) was readily obtained from 1 : 1-diethylsulphonyl-D-*manno*-2 : 3 : 4 : 5 : 6-pentahydroxyhexane (XIII; R = H) by warming it in water, dilute mineral acid, or ethanol for *ca.* 1 min. Zinner and Falk [8] were unable to recrystallise the pentahydroxyhexane (XIII; R = H) owing to its conversion into a compound (m. p. 135°) designated 1 : 1-diethylsulphonyl-D-*arabo*-3 : 4 : 5 : 6-tetrahydroxyhex-1-ene, but without structural proof. The same compound (m. p. 135°) was also prepared by oxidation of D-mannose diethyl dithioacetal in water with 30% hydrogen peroxide. Our syrupy disulphone (X; R = H) failed to crystallise even after several months, but recrystallisation of the pentahydroxyhexane (XIII; R = H) was effected from ethanol containing Cellosolve (2-ethoxyethanol).

The syrupy disulphone (X; R = H) was cleaved by an excess of dilute aqueous ammonia (pH 10—11) to give D-arabinose (XIV) in high yield and diethylsulphonylmethane. As with the cyclic disulphone (IV; R = H), the reaction was appreciably slower than that observed with 1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxypent-1-enes (*e.g.*, VII; R = H), and no orange-red colour developed.[2,3] In contrast, 1 : 1-diethylsulphonyl-D-*manno*-2 : 3 : 4 : 5 : 6-pentahydroxyhexane (XIII; R = H) was extremely sensitive to mild alkali, as were 1 : 1-diethylsulphonyl-D-*galacto*-2 : 3 : 4 : 5 : 6-pentahydroxyhexane (II) already mentioned and the corresponding 6-deoxy-L-*manno*-compound.[3] Paper chromatography with butan-1-ol–pyridine–water as mobile phase caused instantaneous cleavage and only arabinose was detected, whilst the use of either the acidic or the neutral mobile phase gave streaks, presumably because of conversion into the syrupy disulphone (X; R = H) during chromatography. Conversion of the syrupy disulphone (X; R = H) into D-arabinose (XIV) and diethylsulphonylmethane was also effected by prolonged heating at 95—100°, but the degradation ceased before completion owing to the formation of unknown acidic products.

1 : 1-Diethylsulphonyl-D-*manno*-2 : 3 : 4 : 5 : 6-pentahydroxyhexane (XIII; R = H) was oxidised with unbuffered sodium metaperiodate at room temperature in the dark, the expected consumption of 4 mol. of the reagent being obtained with subsequent liberation of 4 equiv. of acid [*i.e.*, 3 mol. of formic acid and 1 mol. of diethylsulphonylacetaldehyde (XVIII) which titrates as a monobasic acid [2]]. Reaction was complete in 1 hr. (see Fig. 1) and is thus analogous to the oxidation of 1 : 1-diethylsulphonyl-L-*manno*-2 : 3 : 4 : 5-tetrahydroxyhexane with sodium metaperiodate.[3] Similarly 1 : 1-diethylsulphonyl-D-*galacto*-2 : 3 : 4 : 5 : 6-pentahydroxyhexane (II) consumed in 1 hr. approximately 4 mol. of sodium metaperiodate. Comparison of these oxidations of acyclic polyhydroxyhexanes (*e.g.*, XIII; R = H) with that of acyclic 1 : 1-diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene (VII; R = H) is of interest. Under unbuffered conditions, the latter showed a fairly rapid consumption of 2 mol. of periodate (1 hr.) followed by a slow overoxidation, a further mol. being consumed (complete in 24 hr.). The slow consumption of the third

mol. of the reagent is probably due to a slow addition of the elements of water across the double bond in the intermediary αβ-unsaturated aldehyde (XVI) to give 1 : 1-diethylsulphonyl-2-hydroxypropionaldehyde (XVII), followed by oxidation in the normal manner to give a second mol. of formic acid and 1 mol. of diethylsulphonylacetaldehyde (XVIII).[2] Thus the same end products are obtained from the oxidation of both saturated and unsaturated acyclic disulphones, but the overall reaction is much slower in the latter cases. Oxidation of 1 : 1-diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene (VI; R = H) at pH 3·56 was slightly quicker (2 mol. of reagent consumed in 35 min.), but the general form of the curve was the same.

Periodate oxidation of D-*talo*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (IV; R = H) under unbuffered conditions showed a fairly rapid consumption of

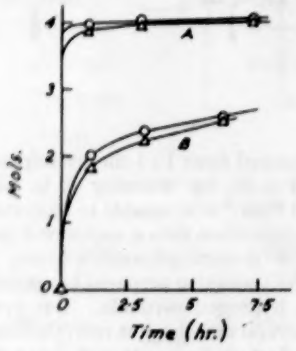
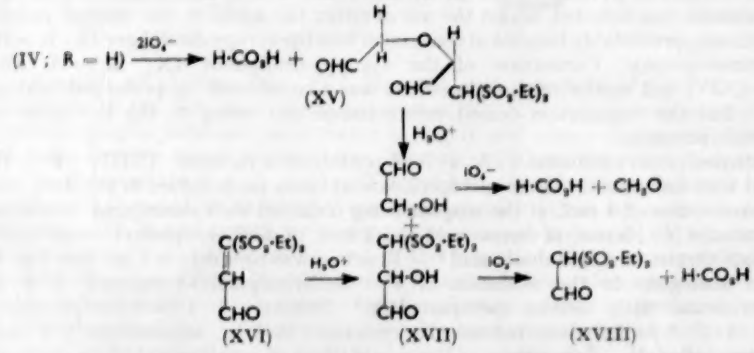


FIG. 1. *Oxidation of* (*A*) 1 : 1-*diethylsulphonyl*-D-manno-2 : 3 : 4 : 5 : 6-*pentahydroxyhexane* (XIII; R = H) *and* (*B*) 1 : 1-*diethylsulphonyl*-D-threo-3 : 4 : 5-*trihydroxypent*-1-*ene* (VII; R = H) *with sodium metaperiodate, without buffer.*

○ *Reagent consumed.* △ *Acid liberated.*

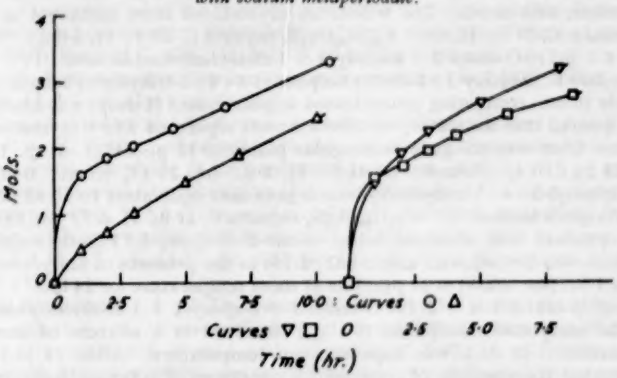
2 mol. of the reagent (2·25 hr.) which was followed by a slower consumption of another 2 mol. (complete in 24 hr.; see Fig. 2). Acid was liberated at a fairly steady rate; at the point where 2 mol. of periodate had been consumed, only 0·98 equiv. of acid had been obtained, but this figure rose to 3·6 equiv. after 24 hr. Thus the rate of liberation of acid during the second stage of the reaction was almost 1·5 times the rate of consumption of periodate. These results indicate that in the first stage the cyclic disulphone (IV; R = H) was oxidised by 2 mol. of periodate to give 1 mol. of formic acid and 1 mol. of the dialdehyde (XV) which was then hydrolysed to give 1 mol. each of glycolaldehyde and 1 : 1-diethylsulphonyl-2-hydroxypropionaldehyde (XVII). Both products would then in the second



stage consume 1 mol. of periodate with the formation from glycollaldehyde of 1 mol. each of formic acid and formaldehyde, and from 1 : 1-diethylsulphonyl-2-hydroxypropionaldehyde (XVII) 1 mol. each of formic acid and diethylsulphonylacetaldehyde (XVIII). Unsuccessful attempts were made to find a pH at which the dialdehyde (XV) would be

stable and so cause oxidation to cease after 2 mol. of periodate had been consumed. At pH 3·56 (see Fig. 2) and lower, the oxidation proceeded as in the unbuffered reaction, whilst at pH 4·6 it was impossible to distinguish between the initial and the second stage. No experiments were carried out at pH > 7 owing to the sensitivity of the cyclic disulphone (IV; R = H) to mild alkali.

FIG. 2. *Oxidation of* D-talo-2 : 6-*epoxy*-1 : 1-*diethylsulphonyl*-3 : 4 : 5-*trihydroxyhexane* (IV; R = H) *with sodium metaperiodate.*



Reagent consumed: ○, *without buffer*; □ *at* pH 3·56; ▽ *at* pH 4·6. △ *Acid liberated, without buffer.*

EXPERIMENTAL

Evaporations were under reduced pressure. Paper chromatography was performed by the descending method at room temperature on Whatman No. 1 filter paper with butan-1-ol–ethanol–water (40 : 11 : 19 v/v), butan-1-ol–pyridine–water (10 : 3 : 3 v/v) or ethyl acetate–acetic acid–water (9 : 2 : 2 v/v) as mobile phase and ammoniacal silver nitrate for the detection of the polyhydroxy-compounds. M. p.s of the disulphones were determined on a Kofler micro-heating stage. Figures quoted for acetyl content have been corrected in order to allow for the extra acid that arises from the sulphone groups during the determination. The " acetyl " contents of the parent unacetylated disulphones were determined, adjusted for molecular weight, and then subtracted from the values obtained for the corresponding acetylated derivatives.

D-talo-2 : 6-*Epoxy*-1 : 1-*diethylsulphonyl*-3 : 4 : 5-*trihydroxyhexane* (IV; R = H).—Aqueous peroxypropionic acid (150% of theory for 4 mol. based on propionic anhydride)[9] was carefully added to a solution of D-galactose diethyl dithioacetal (2·9 g.) in dioxan (20 ml.). The mixture was kept at room temperature for 10 min., then cooled in ice for 1—2 hr. Subsequent concentration yielded white crystals which were dried at 60°/0·05 mm. to remove traces of peroxypropionic acid. Recrystallisation from methanol gave needles (3·1 g., 92%) of D-talo-2 : 6-*epoxy*-1 : 1-*diethylsulphonyl*-3 : 4 : 5-*trihydroxyhexane*, m. p. 193—195°, $[\alpha]_D$ +3·1° (*c*, 1·88 in MeOH), +19·0° (*c*, 2·17 in H_2O), R_F 0·70 (Found: C, 36·4; H, 6·0; S, 19·5. $C_{10}H_{20}O_8S_2$ requires C, 36·2; H, 6·0; S, 19·3%).

D-*Lyxose* (V).—D-*talo*-2 : 6-Epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (1 g.) was shaken in dilute aqueous ammonia (20 ml.; pH 10—11) at room temperature. The mixture remained colourless and paper chromatography indicated that reaction was complete in 7 days. After filtering, the solution was deionised with Amberlite IR-120 (H) and IR-4B (OH) resins and then extracted continually with chloroform for 12 hr. to remove diethylsulphonylmethane. Concentration yielded a pale yellow syrup of D-lyxose (0·42 g., 93%), which co-chromatographed with an authentic specimen in all solvents, and had $[\alpha]_D$ −13·2° (equil.; *c*, 3·80 in H_2O).

D-Lyxose was converted into D-*threo*pentose phenylosazone, m. p. 153—155° not raised on repeated recrystallisation from benzene. Most m. p.s quoted for this compound are in the region of 165°, but Ehrenstein[10] gives m. p. 153—155° (Found: C, 62·0; H, 6·1; N, 17·4. Calc. for $C_{17}H_{20}O_3N_4$: C, 61·9; H, 6·1; N, 17·1%).

[10] Ehrenstein, *Helv. Chim. Acta*, 1926, **9**, 332.

D-talo-3 : 4 : 5-*Tri*-O-*benzoyl*-2 : 6-*epoxy*-1 : 1-*diethylsulphonylhexane* (IV; R = Bz).—D-*talo*-2 : 6-Epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (0·52 g.) in dry pyridine (3 ml.) was treated with benzoyl chloride (0·8 g.), set aside at room temperature for 14 hr., then poured into ice-water; an oil separated and this was extracted with chloroform (100 ml.; 2 × 50 ml.). The extracts were washed with 20% hydrochloric acid, 10% sodium hydrogen carbonate solution, and water, and then dried (Na_2SO_4). Concentration gave a brown syrup (0·61 g.) which was decolorised in the cold in methanol at room temperature. Reconcentration gave a pale brown sludge, which was triturated with a small volume of methanol to a powder. This was filtered off, washed with ether, and dried. The *tribenzoate* crystallised from methanol in plates, m. p. 197—198° (Found: C, 57·7; H, 5·0. $C_{31}H_{32}O_{11}S_2$ requires C, 57·7; H, 5·0%).

D-talo-3 : 4 : 5-*Tri*-O-*acetyl*-2 : 6-*epoxy*-1 : 1-*diethylsulphonylhexane* (IV; R = Ac).—A solution of D-*talo*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (0·25 g.) in acetic anhydride (5 ml.) containing concentrated sulphuric acid (1 drop) was heated at 95—100° for ½ hr., then poured into ice-water; an oily *triacetate* separated which crystallised on stirring. Recrystallisation from ethanol gave rectangular plates (0·15 g., 51%), m. p. 187—188°, $[\alpha]_D$ −21·9° (*c*, 3·23 in $CHCl_3$) [Found: C, 41·7; H, 5·8; Ac, 27·4% (corr.; D-*talo*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane gave acid equivalent to 15·95 acetyl); *M*, 451 (Menzies and Wright's method [11]). $C_{16}H_{26}O_{11}S_2$ requires C, 41·9; H, 5·7; Ac, 28·1%; *M*, 458].

The same product was obtained when D-*talo*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane was treated with acetic anhydride in the presence of anhydrous zinc chloride at 95—100° for 1 hr. (see below) or in pyridine at room temperature for 24 hr.

Treatment of D-talo-3 : 4 : 5-*Tri*-O-*acetyl*-2 : 6-*epoxy*-1 : 1-*diethylsulphonylhexane with Ammonia*.—The acetylated disulphone (0·1 g.), dissolved in a mixture of ammonia (2 ml.; *d*, 0·88) and methanol (2 ml.), was kept at room temperature. After 24 hr., paper chromatography indicated the presence of considerable quantities of D-lyxose, together with a small amount of material (R_y 0·67) which stained with ammoniacal silver nitrate but gave no colour with *p*-anisidine hydrochloride spray. No D-*talo*-2 : 6-epoxy-1 :1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (R_y 0·70) was detected. Subsequent concentration gave a pale yellow syrup which was separated into its components on sheets of Whatman No. 1 filter paper with the neutral solvent as mobile phase. The material (R_y 0·67) was extracted from the appropriate sections of the filter paper with cold methanol, and the extracts were concentrated to a pale yellow syrup. This was acetylated with acetic anhydride containing a trace of sulphuric acid at 95—100° as above and a syrup was isolated which crystallised in several days. Recrystallisation from ethanol gave prisms (14 mg.; m. p. 188—189°), which contained nitrogen, of D-galacto-2-*acetamido*-3 : 4 : 5 : 6-*tetra*-O-*acetyl*-1 : 1-*diethylsulphonylhexane* (VI) (Found: C, 42·3; H, 5·7. $C_{20}H_{33}O_{13}NS_2$ requires C, 42·8; H, 5·9%).

Oxidation of D-*Mannose Diethyl Dithioacetal with Peroxypropionic Acid*.—D-Mannose diethyl dithioacetal (2·4 g.) was oxidised as for D-galactose diethyl dithioacetal. Partial concentration yielded white crystals which were removed by filtering. Complete concentration of the filtrate then gave a syrup (B) from which traces of peroxypropionic acid were removed by repeated dissolution in methanol and reconcentration.

The crystalline product (1·6 g., 52%) was recrystallised from ethanol containing 20% (v/v) of 2-ethoxyethan-1-ol, giving needles of 1 : 1-*diethylsulphonyl*-D-manno-2 : 3 : 4 : 5 : 6-*pentahydroxyhexane* (XIII; R = H) ($C_{10}H_{22}O_9S_2$ requires C, 34·3; H, 6·3. Found: C, 34·3; H, 6·4%). The pentahydroxyhexane (XIII; R = H) was readily (*ca.* 1 min.) converted into the syrup (B) in warm water, dilute mineral acid, ethanol, or methanol. It could not be detected on paper chromatograms; with the basic solvent as mobile phase instantaneous cleavage of the molecule occurred and only the spot characteristic of arabinose was detected, whilst with the acid solvent a streak was obtained presumably due to conversion into the syrupy product during chromatography.

The syrup (B), D-manno-2 : 6-*epoxy*-1 : 1-*diethylsulphonyl*-3 : 4 : 5-*trihydroxyhexane* (X; R = H) (1·1 g., 38%), which was extremely hygroscopic, set to a hard glass on drying (room temp.; 0·05 mm.). It had $[\alpha]_D$ −11·5° (*c*, 8·1 in MeOH), $[\alpha]_D$ +6·3° (*c*, 1·0 in H_2O), R_y 0·57 (Found: C, 35·6; H, 6·0. $C_{10}H_{20}O_8S_2$ requires C, 36·1; H, 6·0%).

D-*Arabinose* (XIV).—D-*manno*-2 : 6-Epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (1 g.) was cleaved with dilute aqueous ammonia (pH 10—11) as for the preparation of D-lyxose. Reaction was complete in 4—5 days and the product (0·40 g., 88%), after recrystallisation from ethanol, had m. p. and mixed m. p. 158—159°, $[\alpha]_D$ −106° (equil.; *c*, 0·93 in H_2O).

[11] Menzies and Wright, *J. Amer. Chem. Soc.*, 1921, **23**, 2309, 2314.

On prolonged heating in water at 95—100°, D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane was partially converted into D-arabinose, but as the reaction proceeded the pH fell to 3—4 and reaction stopped.

D-manno-2 : 3 : 4 : 5 : 6-*Penta*-O-*acetyl*-1 : 1-*diethylsulphonylhexane* (XIII; R = Ac).—The pentahydroxyhexane (X; R = H) (0·18 g.) was heated with acetic anhydride (3 ml.) containing concentrated sulphuric acid (1 drop) at 95—100° for ½ hr. Oily acetylated material, which separated when the mixture was poured into ice-water, was extracted into chloroform (2 × 30 ml.), and the extracts were washed with sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$). Concentration of the chloroform solution then gave a pale yellow syrup (0·17 g., 60%) which crystallised overnight. Recrystallised from a minimum of ethanol, the *penta-acetate* had m. p. 147—150° [Found : C, 42·5; H, 5·7; S, 10·5; Ac, 37·9 (corr.); 1 : 1-diethylsulphonyl-D-*manno*-2 : 3 : 4 : 5 : 6-pentahydroxyhexane gave acid equivalent to 7·13% acetyl). $C_{20}H_{32}O_{14}S_2$ requires C, 42·8; H, 5·7; S, 11·4; Ac, 38·4%].

D-manno-3 : 4 : 5-*Tri*-O-*acetyl*-2 : 6-*epoxy*-1 : 1-*diethylsulphonylhexane* (X; R = Ac).—The syrup (B) (X; R = H) (0·50 g.), obtained from the oxidation of D-mannose diethyl dithioacetal, was heated with acetic anhydride (4 ml.) and anhydrous zinc chloride (0·1 g.) at 95—100° for 1 hr. The product was worked up as above and concentration of the chloroform extracts gave a pale yellow syrup (0·49 g., 70%) of the *tri*-O-*acetyl compound* which crystallised in 4—5 months. It was drained on a tile and washed with benzene and a little ether, then having m. p. 125—127° [Found : C, 41·6; H, 5·7; S, 14·7; Ac, 26·7 (corr.). $C_{16}H_{24}O_{11}S_2$ requires C, 41·9; H, 5·7; S, 14·0; Ac, 28·1%].

Treatment of D-manno-3 : 4 : 5-*Tri*-O-*acetyl*-2 : 6-*epoxy*-1 : 1-*diethylsulphonylhexane with Ammonia.*—A solution of D-*manno*-3 : 4 : 5-tri-*O*-acetyl-2 : 6-epoxy-1 : 1-diethylsulphonylhexane (0·32 g.) in methanol (6 ml.) and ammonia (*d* 0·88; 6 ml.) was kept at room temperature for 24 hr., after which paper chromatography indicated the presence of large amounts of arabinose and a small amount of faster-running material. The latter material gave no colour with the *p*-anisidine hydrochloride spray or with ninhydrin, but was shown by ammoniacal silver nitrate and gave a green colour with the Elson–Morgan reagent.[12] The solution was concentrated to a syrup which was separated into its components on sheets of Whatman No. 1 filter paper with the acid solvent as mobile phase. The faster-moving material was eluted from the appropriate sections of the filter paper with warm methanol, and the extracts were concentrated to a syrup. This was acetylated with acetic anhydride containing a trace of sulphuric acid at 95—100° as above, and a syrup was isolated which was triturated with ether to a powder. Crystallisation from ether gave crystals (21 mg.) of D-*gluco*-2-acetamido-3 : 4 : 5 : 6-tetra-*O*-acetyl-1 : 1-diethylsulphonylhexane [4] (XI), m. p. and mixed m. p. 178—179° (Found : C, 43·0; H, 5·7; N, 2·5. Calc. for $C_{20}H_{33}O_{13}S_2N$: C, 42·8; H, 5·9; N, 2·5%).

D-manno-2 : 6-*Epoxy*-1 : 1-*diethylsulphonyl*-3 : 4 : 5-*trihydroxyhexane* (X; R = H) *from* D-*Glucose Diethyl Dithioacetal.*—D-Glucose diethyl dithioacetal (0·67 g.) was oxidised as for D-galactose diethyl dithioacetal. Concentration of the mixture gave a hygroscopic syrup (A) (0·72 g., 93%) which was freed from traces of peroxypropionic acid by repeated dissolution in methanol and reconcentration. The syrup set on prolonged drying (room temp.; 0·05 mm.) to a hard glass, $[\alpha]_D$ −13·1° (*c*, 4·4 in MeOH), R_F 0·57, co-chromatographing with the syrup obtained on oxidation of D-mannose diethyl dithioacetal.

D-manno-3 : 4 : 5-*Tri*-O-*benzoyl*-2 : 6-*epoxy*-1 : 1-*diethylsulphonylhexane* (X; R = Bz).—D-*manno*-2 : 6-Epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (0·25 g.) (syrup B) was benzoylated as for the corresponding D-*talo*-compound (IV; R = H), and a pale brown syrup (0·36 g.) was isolated which was triturated to a fine powder with methanol–ether. Crystallised from methanol–ether the *tri*-O-*benzoyl derivative* (X; R = Bz) had m. p. 87—90° (Found : C, 57·4; H, 5·0. $C_{31}H_{32}O_{11}S_2$ requires C, 57·7; H, 5·0%).

Benzoylation of a sample of D-*manno*-2 : 6-epoxy-1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxyhexane (syrup A) gave the same tri-*O*-benzoyl derivative (X; R = Bz) with m. p. 87—91°, mixed m. p. 86—91°, *X*-ray powder photographs of the two compounds being identical (Found : C, 57·9; H, 5·0%).

Periodate Oxidation of the Diethylsulphones derived from D-*Galactose,* D-*Mannose, and* D-*Glucose.*—(i) *Uptake.* A mixture of *ca.* 0·3M-sodium metaperiodate, acetate buffer (25 ml.), and disulphone (60—90 mg., weighed accurately) was made up to 100 ml. and stored in an amber bottle in the dark. A control containing none of the disulphone was worked concurrently. At intervals, the periodate uptake was estimated [13] by transferring samples (10 ml. each) from the

[12] Partridge, *Biochem. J.*, 1948, **42**, 238.
[13] Neumüller and Vasseur, *Arkiv Kemi*, 1953, **5**, 235.

oxidation mixture and control, into a mixture of phosphate buffer (pH 7·0; 30 ml.) and 20% potassium iodide solution (5 ml.), then titrating the liberated iodine with 0·01N-sodium thiosulphate (starch indicator).

(ii) *Total acidity.* Solutions of the oxidation mixture and control were prepared as above, but without the acetate buffer. Acid was determined [14] by taking samples (10 ml. each) from the oxidation mixture and control, adding ethylene glycol (2 ml.) to each, and after 5 min. (to ensure complete destruction of the excess of periodate), titrating with 0·01N-sodium hydroxide (methyl-red, screened with methylene-blue). Results are given in the Figs.

We thank Dr. T. Bevan for the *X*-ray powder photographs and one of us (T. J. T.) thanks the Department of Scientfic and Industrial Research for a Maintenance Allowance.

THE UNIVERSITY, BRISTOL. [*Received, August 29th*, 1955.]

[14] Halsall, Hirst, and Jones, *J.*, 1947, 1427.

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204. *A New Mechanism for the Beckmann Rearrangement of Ketoximes.*

By HENRY STEPHEN and BENJAMIN STASKUN.

Based on experimental observations, a new mechanism is proposed for the Beckmann rearrangement involving the formation of a ketoxime anhydride by dehydration of two molecules of the ketoxime. The anhydride rearranges to give the ketoxime imidate which further rearranges forming the imidoyl anhydride which in the presence of hydrogen chloride gives an imidoyl chloride and an amide in equimolecular proportions.

IT is generally accepted that if a ketoxime is treated with certain acidic reagents such as thionyl chloride,[1] phosphorus pentachloride,[2] phosphorus oxychloride,[2] or benzenesulphonyl chloride,[3] and the product treated with water, a substituted amide is obtained. It has now been established that the substituted amide is produced during the rearrangement in the complete absence of water, and the present investigation has further shown that any of the above reagents (1 mol.) rearranges a ketoxime (2 mols.) to yield the corresponding amide and imidoyl chloride in approximately equimolecular amounts. It is of interest that in the rearrangement of the oximes of acetophenone and 2-acetylnaphthalene the isomeric amides separate as hydrochlorides (37%) from the chloroform solutions, the imidoyl chlorides (37%) remaining in solution. With these exceptions, the proportions of reactants stated above gave equimolar mixtures of the products in solution; these were identified, and their respective yields ascertained, by converting the imidoyl chlorides into (*a*) amidines by treatment with gaseous ammonia, and (*b*) 2 : 3-disubstituted quinazol-4-ones by condensation with methyl anthranilate,[4] and separation of the bases in each case from the amide by treatment with acid. The 3-substituent in the quinazolone is that radical of the ketoxime which has migrated during the rearrangement. Phosphorus pentachloride differs from the other reagents in that, if more than ½ mol. is used per mol. of ketoxime, the excess reacts with the amide to form more imidoyl chloride: $R{\cdot}CO{\cdot}NHR + PCl_5 \longrightarrow R{\cdot}CCl{:}NR + POCl_3 + HCl$; with 1 mol. each of benzophenone oxime with phosphorus pentachloride, the amount of imidoyl chloride formed is sufficient to yield 80% of 2 : 3-diphenylquinazol-4-one, whereas only 40% of it is obtained with ½ mol. of phosphorus pentachloride. It is now clear why Beckmann [1] and Coleman and Pyle,[5] who used equimolecular proportions, obtained only *N*-phenylbenzimidoyl chloride as the penultimate product, and benzanilide after treatment with water. It is worth noting that the action of phosphorus pentachloride (1 mol.) on a ketoxime (1 mol.) in anhydrous chloroform is useful for the preparation of imidoyl chlorides which can be used ***in situ*** for the preparation of amidines and quinazol-4-ones in good yields.

[1] Stephen and Bleloch, *J.*, 1931, 886.
[2] Beckmann, *Ber.*, 1886, **19**, 988.
[3] Kuhara, *Mem. Coll. Sci., Kyoto Univ.*, 1917, **3**, 1.
[4] Levy and Stephen, following paper.
[5] Coleman and Pyle, *J. Amer. Chem. Soc.*, 1946, **68**, 2007.

During the rearrangement of ketoximes a characteristic yellow colour develops, and it is suggested that this is associated with the presence of a ketoxime benzimidate (III) such as the yellow compound (III; R = Ph) prepared by Chapman.[6] Alkyl aryl ketoximes undergo a further colour change, to deep red, which appears to be due to the action of excess of the reagent on amides of the type R·NH·COMe, usually resulting in a tar.

Chapman [6] observed that *N*-phenylbenzimidoyl chloride (0·002 mol.) in the presence of hydrogen chloride rearranges benzophenone oxime almost quantitatively, but that in the absence of hydrogen chloride only 10% conversion takes place. The efficacy of the chloride in rearranging benzophenone oxime is shown (p. 985) when 2 c.c. of a rearranged solution of benzophenone oxime containing the chloride (0·005 g.) and no thionyl chloride is added to a solution of benzophenone oxime (2 g.) in chloroform saturated with hydrogen chloride; this effects 15% rearrangement of the oxime to benzanilide. Similarly when a trace (0·06 mol.) of various other reagents (Table 3) is used, the imidoyl chloride first formed continues the rearrangement in the presence of hydrogen chloride after the reagent has been exhausted. As the rearrangement proceeds the amount of amide produced becomes greater and the ratio of imidoyl chloride to amide decreases as long as unchanged oxime is present. It therefore becomes possible to produce amide as the chief product of rearrangement. Although hydrogen chloride is essential during the rearrangement, there is no rearrangement when an oxime hydrochloride is refluxed in chloroform solution. During the rearrangement of ketoximes in chloroform with traces of reagent, the only hydrogen chloride available is that produced by the reaction between the reagent and the ketoxime, but this is insufficient for the maximum rearrangement of certain ketoximes (see Table 1). Maximum rearrangement can be attained by saturating the chloroform solution of the ketoxime and a trace of reagent with dry hydrogen chloride (see Table 3).

The mechanism now proposed for the Beckmann rearrangement of ketoximes is an attempt to explain (*a*) the formation of equimolecular amounts of imidoyl chloride and amide during from 2 : 1 molecular proportions of ketoxime and reagent, and (*b*) the almost quantitative conversion of ketoximes into amides by traces of reagent in presence of hydrogen chloride. The first stage is dehydration of the ketoxime to ketoxime anhydride (I), which is symmetrical and would not be expected to rearrange spontaneously. Addition of hydrogen chloride disturbs the symmetry, forming the salt (II). The electromeric effect arising from the attachment of a proton to one of the nitrogen atoms causes the cation of (II) to rearrange to the ketoxime imidate (III) in a manner similar to the rearrangement of the picryl ethers and benzenesulphonyl esters of ketoximes. Chapman [6] showed that benzophenone oxime *N*-phenylbenzimidate (III; R = H) rearranges in presence of hydrogen chloride in anhydrous ether to *N*-phenylbenzimidoyl chloride and benzanilide in approximately equimolecular proportions and suggested that the ester was formed by the reaction :

$$Ph_2C{:}N{\cdot}OH + Ph{\cdot}CCl{:}NPh \longrightarrow Ph_2C{:}N{\cdot}O{\cdot}CPh{:}NPh$$

However, since the ester is readily decomposed by hydrogen chloride at room temperature it is not likely to be produced by the condensation of the oxime and the imidoyl chloride. The present authors are of the opinion that the formation of the ester (III) is, nevertheless, an essential part of the Beckmann rearrangement and that it is produced by rearrangement of the ketoxime anhydride in presence of hydrogen chloride. The ester then rearranges to the imidoyl anhydride (IV), which decomposes in the presence of hydrogen chloride to give equimolecular amounts of imidoyl chloride and amide :

$$R_2C{:}N{\cdot}OH \xrightarrow{\text{Reagent}} \underset{\text{(I)}}{(R_2C{:}N{\cdot})_2O} \xrightarrow{HCl} \underset{\text{(II)}}{[R_2C{:}NH^+{\cdot}O{\cdot}N{:}CR_2]Cl^-} \longrightarrow$$

$$\underset{\text{(III)}}{R{\cdot}N{:}CR{\cdot}O{\cdot}N{:}CR_2} \longrightarrow \underset{\text{(IV)}}{(R{\cdot}N{:}CR{\cdot})_2O} \xrightarrow{HCl} R{\cdot}CCl{:}NR + R{\cdot}CO{\cdot}NHR$$

This mechanism can be applied when traces of the reagent are used, provided that in the initial stage there is sufficient to form a trace of the ketoxime anhydride (I) in presence of

[6] Chapman, *J.*, 1935, 1223.

hydrogen chloride. The rearrangment of anhydride will take place as above with formation of the imidoyl chloride which can then dehydrate the ketoxime to (I), forming the amide at the same time:

$$2R_2C{:}N{\cdot}OH + R{\cdot}CCl{:}NR \longrightarrow (R_2C{:}N{\cdot})_2O + R{\cdot}CO{\cdot}NHR + HCl$$

The yield of amide thus increases at the expense of the chloride.

The formation of amidines during the rearrangement of ketoximes was first demonstrated by Stephen and Bleloch,[1] and the mechanism for their formation as suggested by Chapman [6] is from the imidoyl anhydride (IV) which can undergo an intramolecular

$$\underset{\text{(IV)}}{(R{\cdot}N{:}CR{\cdot})_2O} \longrightarrow \underset{\text{(V)}}{R{\cdot}CO{\cdot}NH{\cdot}CR{:}NR} \longrightarrow R{\cdot}CO_2H + R{\cdot}NH{\cdot}CR{:}NR$$

$$\text{(VI)}\quad HN{:}CR{\cdot}O{\cdot}COR \longrightarrow (R{\cdot}CO)_2NH \quad \text{(VII)}$$

change to the acylamidine (V). The change of (IV) ⟶ (V) is analgous to the change of the imidoyl anhydride (VI) to the diacylamine (VII) investigated by Mumm, Hesse, and Volquartz.[7]

Other reagents used for the Beckmann rearrangement of ketoximes, such as zinc chloride, ferric chloride, or aluminium chloride,[8] may function as dehydrating agents for the formation of the anhydride (I).

Experimental

Apparatus and reagents were carefully dried. The oximes were stored over phosphoric oxide. The chloroform was heated with phosphoric oxide for 1 hr. and then distilled.

Rearrangement of Acetophenone Oxime (1 *mol.*) *by Reagent* (1 *mol.*).—To this oxime (2·7 g.) in anhydrous chloroform (40 c.c.), thionyl chloride (1·5 c.c.) in anhydrous chloroform (5 c.c.) was added. The solution warmed to 35°, sulphur dioxide and hydrogen chloride being evolved. Dry hydrogen chloride was passed into the solution until it acquired a deep yellow colour (1—2 hr.) and acetanilide hydrochloride separated. On cooling in ice for a further 1—2 hr., the colour changed from yellow to deep red. Acetanilide hydrochloride was filtered off, washed with dry chloroform (5—10 c.c.), and dried (P_2O_5) (yield, 1·3 g., 38%). The filtrate and washings were distilled under reduced pressure; the residue was extracted with N-sodium hydroxide to remove unchanged oxime, and then with N-hydrochloric acid. The residue of crude acetanilide was crystallised from the minimum volume of boiling water, leaving a small quantity of tar. The acid extract, on being made ammoniacal, deposited diphenylacetamidine (0·2 g.) which after crystallisation from methanol had m. p. and mixed m. p. 131—132°. Unchanged oxime (0·45 g.), m. p. 52—56°, was recovered on acidification of the sodium hydroxide extract. The yield of acetanilide (0·98 g.), m. p. and mixed m. p. 112—113°, was 36%.

When a solution of acetanilide (2·7 g.) in dry chloroform (40 c.c.) was warmed with thionyl chloride (1·5 c.c.) its colour changed to deep red and acetanilide hydrochloride was deposited. After removal of chloroform the residue yielded acetanilide and a tar.

β-Acetonaphthalide behaved similarly with thionyl chloride in chloroform.

The product, which crystallised during the rearrangement of acetophenone oxime, was practically colourless and when freshly prepared and dry had m. p. 120—125° (decomp.). On storage it lost hydrogen chloride and yielded acetanilide. On treatment with water it yielded acetanilide, m. p. 112—113°, and hydrochloric acid. Two unstable hydrochlorides, $(NHPhAc)_2,HCl$ and NHPhAc,HCl, are known.[9,10] Titration of the aqueous filtrate with 0·1N-sodium hydroxide indicates that the 1 : 1 salt was obtained during the rearrangement, though, owing to instability, the experimental values for chloride are low (Found: HCl, 20·3. Calc. for C_8H_9ON,HCl: HCl, 21·3%).

2-Methyl-3-phenylquinazol-4-one.—Acetophenone oxime (2·7 g.) was rearranged as above and acetanilide hydrochloride (1·3 g., 38%) removed. To the chloroform filtrate and washings, methyl anthranilate (12 c.c.) was added and the mixture kept at room temperature for 12 hr., made alkaline with aqueous ammonia, and steam-distilled, leaving crude quinazolone, m. p. 137—142° (1·46 g., 31%). Recrystallisation from methanol gave colourless crystals, m. p. and mixed m. p. 144—146°.

[7] Mumm, Hesse, and Volquartz, *Ber.*, 1915, **48**, 379.
[8] Beckmann and Bark, *J. prakt. Chem.*, 1923, **105**, 327.
[9] Dehn, *J. Amer. Chem. Soc.*, 1912, **34**, 1904.
[10] Ephraim and Hochuli, *Ber.*, 1915, **48**, 634.

To acetophenone oxime (2·7 g.) in dry chloroform, powdered phosphorus pentachloride (2·08 g.) was added with shaking till all the reagent had dissolved (5 min.). The clear yellow solution was kept at room temperature for 3—4 hr. but no acetanilide hydrochloride separated. Methyl anthranilate (20 c.c.) was added and after a further 12 hr. the mixture was treated as above, yielding 2-methyl-3-phenylquinazol-4-one (3·45 g., 71%), m. p. 140—145°.

Rearrangement of 2-Acetylnaphthalene Oxime.—The oxime (3·7 g.), suspended in dry chloroform (60 c.c.), was rearranged with thionyl chloride (1·5 c.c.) as described above. β-Acetonaphthalide hydrochloride was deposited (1·7 g., 39·2%) (Found: HCl, 15·5. Calc. for $C_{12}H_{11}ON,HCl$: HCl, 16·5%); with water it gave β-acetonaphthalide, m. p. and mixed m. p. 131—132°. The chloroform filtrate and washings, after steam-distillation, yielded material (2·15 g.), m. p. 115—124°. Fractional crystallisation from methanol separated unchanged oxime (0·5 g.) from β-acetonaphthalide (1·5 g., 40%), leaving a small quantity of tar. The acid filtrate on being made ammoniacal did not deposit amidine.

To the oxime (1·32 g.) in chloroform (30 c.c.) phosphorus oxychloride (0·7 c.c., 1 mol.) was added without cooling. After 12 hr. the clear yellow solution was saturated with hydrogen chloride; it deposited β-acetonaphthalide hydrochloride (0·56 g.), which with water gave β-acetonaphthalide, m. p. 130—131° (0·5 g., 38%).

2-Methyl-3-β-naphthylquinazol-4-one.—2-Acetylnaphthalene oxime (3·7 g.) was rearranged with thionyl chloride as above. β-Acetonaphthalide hydrochloride (1·7 g., 39%) was filtered off and the filtrate treated with excess of methyl anthranilate (12 c.c.) and allowed to remain for 12 hr. 2-Methyl-3-β-naphthylquinazol-4-one (1·9 g., 32%), m. p. and mixed m. p. 174—175°, was obtained as above.

The best yield (71%) of the quinazolone was obtained by shaking a cold suspension of the oxime (1·85 g.) in dry chloroform with phosphorus pentachloride (2·08 g.) for 5 min. and allowing the yellow solution to remain at room temperature for 2 hr. The solution, cooled in ice, was then treated with methyl anthranilate (15 c.c.) and kept for 12 hr. and worked up as above, yielding the quinazol-4-one (2·03 g.), m. p. 174—175°.

Rearrangement of Benzophenone Oxime.—To a solution of the oxime (1·97 g.) in dry chloroform (40 c.c.), thionyl chloride (0·8 c.c.) in dry chloroform (10 c.c.) was added. Hydrogen chloride and sulphur dioxide were evolved from the clear solution, the temperature rising to 20°, and the solution rapidly became yellow. After 12 hr. the solution was saturated with dry ammonia and kept for 1 hr. Ammonium chloride formed was filtered off and the chloroform filtrate distilled under reduced pressure, leaving a yellow residue (1·9 g.). This product was warmed with N-hydrochloric acid to dissolve phenylbenzamidine. The insoluble benzanilide (0·95 g., 48%), after crystallisation, had m. p. and mixed m. p. 161—162°. The acid filtrate, on being made ammoniacal, deposited phenylbenzamidine (0·9 g., 45%), recrystallisation giving the pure product, m. p. and mixed m. p. 111—113°.

2 : 3-Diphenylquinazol-4-one.—To a solution of benzophenone oxime (1·97 g.) rearranged with thionyl chloride (0·8 c.c.), methyl anthranilate (10 c.c.) was added and the mixture left at room temperature for 12 hr. The residue, after treatment with ammonium hydroxide and steam-distillation, was warmed with N-hydrochloric acid (40 c.c.) and filtered. Benzanilide (0·9 g., 45%), m. p. 161—162°, was obtained from the insoluble residue, and the acidic filtrate, when made ammoniacal, deposited the quinazolone (1·8 g., 40%). After crystallisation from methanol, this had m. p. and mixed m. p. 158—159°.

To a solution of benzophenone oxime (1·97 g.) in chloroform (50 c.c.) phosphorus pentachloride (2·08 g.) was added. After 2 hr. methyl anthranilate (15 c.c.) was added and the mixture treated as above. The quinazol-4-one (2·3 g., 80%) and a trace of benzanilide (0·2 g.) were obtained.

2-Methyl-3-p-tolylquinazol-4-one.—To a cold solution of 4-methylacetophenone oxime (1·49 g.), dissolved in dry chloroform (50 c.c.), phosphorus pentachloride (2·08 g.) was added rapidly. The yellow solution was cooled in ice and methyl anthranilate (15 c.c.) added. After 12 hr. at room temperature aqueous ammonia was added, and the mixture steam-distilled. The residue was treated with concentrated hydrochloric acid and filtered and the filtrate made alkaline to liberate the base which crystallised from methanol as pale yellow needles, m. p. and mixed m. p. 148—150° (1·73 g., 69%).

Rearrangement of Ketoximes (2 mol.) with Reagent (1 mol.).—(*a*) Acetophenone oxime (2·7 g.) was rearranged with thionyl chloride (0·8 c.c.) as above. Acetanilide (1·0 g., 37%) separated as the hydrochloride; and a further 1 g. (37%) was obtained from the chloroform filtrate together with unchanged oxime (0·4 g.) and diphenylacetamidine (0·05 g.). No tar was produced.

(*b*) 2-Acetylnaphthalene oxime (1·85 g.) was rearranged with phosphorus pentachloride

(1·04 g.). β-Acetonaphthalide hydrochloride (0·88 g., 40%) separated and the chloroform filtrate yielded β-acetonaphthalide (0·76 g., 40%) and unchanged oxime (0·45 g.).

(*c*) A solution of benzophenone oxime (1·97 g.), rearranged with thionyl chloride (0·4 c.c.), was treated with methyl anthranilate (10 c.c.), yielding the previous products in the same proportions.

A solution of benzophenone oxime (1·97 g.) in dry chloroform (50 c.c.) was rearranged with phosphorus pentachloride (1·04 g.) and saturated with dry ammonia. The product yielded benzanilide (0·9 g., 45%), and phenylbenzamidine (0·9 g., 45%).

Rearrangement of Ketoximes with Traces of Reagent.—(*a*) When a solution of the hydrochloride of acetophenone oxime, 2-acetylnaphthalene oxime, or benzophenone oxime in dry chloroform was refluxed, hydrogen chloride was evolved. The solutions remained clear and colourless, and, after removal of the chloroform, the residue in each case yielded only unchanged oxime.

(*b*) When a ketoxime (1 mol.) in dry chloroform (40 c.c.) was refluxed with thionyl chloride (0·06 mol.) for ½ hr. a characteristic yellow colour developed, but with acetophenone oxime very gradually. After removal of the chloroform, the amides were obtained as reported in Table 1.

(*c*) The rearrangements of ketoxime hydrochlorides (1 mol.) with thionyl chloride (0·06 mol.) carried out as described above are recorded in Table 2.

(*d*) When a solution of ketoxime (1 mol.) in dry chloroform (40 c.c.) was saturated with dry hydrogen chloride, treated with thionyl chloride (0·06—0·11 mol.), and left at room-temperature, the yields of amides were as given in Table 3.

(*e*) Table 4 gives results obtained when benzophenone oxime hydrochloride (2·34 g.) in dry chloroform (40 c.c.) was rearranged with traces of various reagents (0·06 mol.) on refluxing the solution for ½ hr. After removal of the chloroform, any unchanged oxime was separated from the benzanilide by the method given by Chapman.[6]

(*f*) Acetophenone oxime hydrochloride (2 g.) in dry chloroform (60 c.c.) was rearranged with a trace of reagent (0·06 mol.). The mixtures were saturated with hydrogen chloride and left for 48 hr. Acetanilide hydrochloride was filtered off and dried. The chloroform filtrates were treated as usual, and acetanilide in solution was separated from unchanged oxime. The results are given in Table 5.

(*g*) To 2-acetylnaphthalene oxime (1·85 g.) in dry chloroform (40 c.c.) thionyl chloride (0·06 mol.) was added, and the mixture saturated with dry hydrogen chloride and left for 48 hr. β-Acetonaphthalide hydrochloride (1·8 g., 80%) separated and the chloroform filtrate yielded β-acetonaphthalide (0·1 g., 5%) and a small amount of unchanged oxime.

(*h*) A rearranged solution of benzophenone oxime hydrochloride (2·34 g.) in dry chloroform (40 c.c.) with thionyl chloride (3 drops) (cf. *b*) was saturated with dry ammonia and left for

TABLE 1.

Ketoxime	Amide	M. p.	Yield (%)
$Ph_2C{:}N{\cdot}OH$	NHPhBz	160°	97
$(p\text{-}C_6H_4Cl)_2C{:}N{\cdot}OH$	$C_6H_4Cl{\cdot}CO{\cdot}NH{\cdot}C_6H_4Cl$	210	29
$p\text{-}C_6H_4Cl{\cdot}CPh{:}N{\cdot}OH$	Ar·NH·COAr (mixed)	—	56
$PhMeC{:}N{\cdot}OH$	NHPhAc	112	7

TABLE 2.

Ketoxime	Amide	M. p.	Yield (%)
$Ph_2C{:}N{\cdot}OH$	NHPhBz	160°	97
$(p\text{-}C_6H_4Me)_2C{:}N{\cdot}OH$	NHAr·COAr	159	96
$(p\text{-}C_6H_4Cl)_2C{:}N{\cdot}OH$	,,	210	35
$p\text{-}C_6H_4Cl{\cdot}CPh{:}N{\cdot}OH$	Mixed	—	90
$(CH_2Ph)_2C{:}N{\cdot}OH$	$CH_2Ph{\cdot}NH{\cdot}CO{\cdot}CH_2Ph$	—	Trace
$PhMeC{:}N{\cdot}OH$	NHPhAc	112	13
$2\text{-}C_{10}H_7{\cdot}CMe{:}N{\cdot}OH$	$2\text{-}C_{10}H_7{\cdot}NHAc$	130	6

TABLE 3.

Ketoxime	$SOCl_2$ (mol.)	Time (hr.)	Yield of amide (%)	Ketoxime	$SOCl_2$ (mol.)	Time (hr.)	Yield of amide (%)
$CPh_2{:}N{\cdot}OH$	0·06	0·25	75	$(CH_2Ph)_2C{:}N{\cdot}OH$	0·11	96	32
	—	3·0	97	$2\text{-}C_{10}H_7{\cdot}CMe{:}N{\cdot}OH$ ...	0·11	72	82
$PhMeC{:}N{\cdot}OH$ ...	0·06	24	59	$p\text{-}C_6H_4Me{\cdot}CMe{:}N{\cdot}OH$	0·09	24	83
	0·09	48	90	$(p\text{-}C_6H_4Me)_2C{:}N{\cdot}OH$	0·06	1	97

TABLE 4.

Reagent	Yield of NHPhBz (%)	Oxime recovered (%)	Reagent	Yield of NHPhBz (%)	Oxime recovered (%)
$SOCl_2$ *	95	0	CCl_3·CHO	0	89
PCl_5 *	97	0	CPh_3Cl	0	86
$POCl_3$ *	91	0	P_2O_5	4	89
Ph·SO_2Cl	67	27·5	H_2SO_4	0	87
AcCl	0	91	$AlCl_3$	0	78
Ac_2O	0	87			

* Yellow colour developed on refluxing.

TABLE 5.

Reagent	Yield (%) of NHPhAc,HCl	Yield (%) of R·CCl:NR	Unchanged oxime (g.)	Reagent	Yield (%) of NHPhAc,HCl	Yield (%) of R·CCl:NR	Unchanged oxime (g.)
$SOCl_2$ ...	80	8	0·75	Ph·SO_2Cl ...	65	13	0·5
PCl_5	75	10	0·5				

12 hr. The product yielded phenylbenzamidine (0·1 g.), corresponding to the *N*-phenylbenzimidoyl chloride in solution, and benzanilide (1·8 g.). The rearranged solution, therefore, contained no more than 0·0025 g. of imidoyl chloride, and 0·045 g. of benzanilide per c.c., and no thionyl chloride.

(*i*) A similarly rearranged solution (2 c.c.) was added to benzophenone oxime hydrochloride (2·34 g.) in dry chloroform (40 c.c.), and the mixture saturated with dry hydrogen chloride and refluxed for 1 hr. Benzanilide (0·41 g.) and unchanged oxime (1·62 g.) were obtained. Since the 2 c.c. of the rearranged solution added contained about 0·1 g. of benzanilide, rearrangement was approx. 15% complete.

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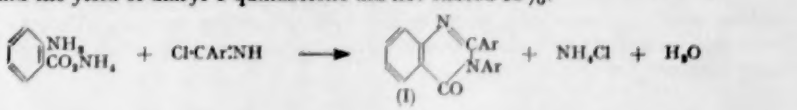
205. *Syntheses in the Quinazolone Series. Part I. Synthesis of 2 : 3-Diaryl-4-quinazolones.*

By PAUL R. LEVY and HENRY STEPHEN.

2 : 3-Diaryl-4-quinazolones may be prepared in good yields (i) by condensation of *N*-arylbenzimidoyl chloride with ammonium anthranilate or methyl anthranilate, and (ii) by reduction of *N*-aroyl-*o*-nitrobenzamides.

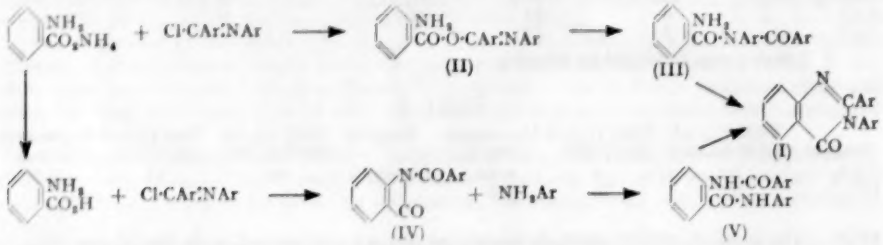
MUMM AND HESSE[1] obtained 2 : 3-diphenyl-4-quinazolone by treating a solution of *N*-phenylbenzimidoyl chloride in ether with aqueous sodium anthranilate. The method is unsuitable for general application, since the imidoyl chlorides are rapidly hydrolysed by water, giving quinazolones in low yield. The procedure was modified by condensing ammonium anthranilate with an *N*-arylbenzimidoyl chloride in acetone, in which both reactants are soluble, the progress of the reaction being indicated by the deposition of ammonium chloride. The weight of the latter did not correspond with the following reaction and the yield of diaryl-4-quinazolone did not exceed 35%.



A mixture of the quinazolone (I) with 30% of an *o*-aroylamino-*N*-arylbenzamide (V) was obtained in every case investigated, and in addition some *NN'*-diarylbenzamidine and a primary aromatic amine. The formation of the various compounds indicates

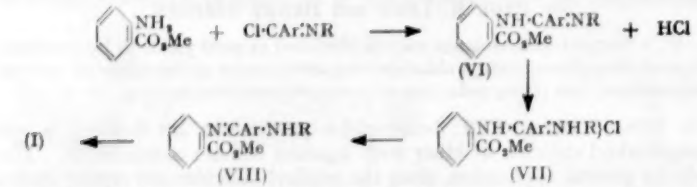
[1] Mumm and Hesse, *Ber.*, 1910, **43**, 2508.

that two reactions are taking place: condensation of benzimidoyl chloride with ammonium anthranilate to give the quinazolone (I), and with anthranilic acid to give the diamide (V). The second reaction is due to formation of anthranilic acid through the dissociation of ammonium anthranilate, which is appreciable in dry acetone even at 0°, and at higher temperatures the salt is almost completely dissociated.



The formation of the diacylamine (III) by isomeric change of compounds of the type (II) has been established by Mumm and Hesse,[1] and the present investigation has shown that the condensation of the diacylamine (III) to give the quinazolone (I) takes place rapidly in acetone. The reaction between anthranilic acid and *N*-phenylbenzimidoyl chloride was also investigated by Mumm and Hesse,[1] who obtained benzoylanthranil (IV), aniline, and diphenylbenzamidine. The formation of *o*-benzamido-*N*-phenylbenzamide (V) by the action of aniline on benzoylanthranil at 170° is known.[2] The present investigation, however, has shown that diamides (V) and similar compounds are readily formed by the addition of primary aromatic amines to benzoylanthranil in acetone at 50°. The formation of the diamide (V) can be obviated by adding solid ammonium anthranilate to a solution of benzimidoyl chloride in dry acetone. The dissociation of ammonium anthranilate is minimised and a 70% yield of quinazolone is obtained.

N-Arylbenzimidoyl chlorides (1 mol.) condense with methyl anthranilate (2 mol.) in acetone rapidly at room temperature, yielding 80—90% of the 2 : 3-diarylquinazolone (the additional mol. of methyl anthranilate is used to combine with hydrogen chloride liberated). Less than 2 mol. of methyl anthranilate give a low yield of the quinazolone. It is assumed that the amidine (VI) is first formed and undergoes the well-known tautomeric



change to (VIII), the structure of which is now suitable for ring formation by elimination of methyl alcohol to give the quinazolone (I). The interconversion (VI) ⟶ (VIII) takes place by electromerisation of the cation of the salt (VII). This part of the investigation is being extended.

N-Aroyl-*o*-nitrobenzamides (IX) are readily prepared in good yields by condensing sodium *o*-nitrobenzoate with an arylimidoyl chloride in dry acetone. They are smoothly reduced by sodium dithionite in alcohol, to the diarylamines (III) which undergo immediate ring closure to the quinazolones (I).

[1] (*a*) Anschütz, Schmidt, and Greiffenberg, *Ber.*, 1902, **35**, 3480; (*b*) Bogert *et al.*, *J. Amer. Chem. Soc.*, 1905, **27**, 6561; 1911, **33**, 949.

Experimental

The following imidoyl chlorides were obtained by the action of phosphorus pentachloride [3] or thionyl chloride [4] on the aroylamine: N-o-*methoxyphenylbenzimidoyl chloride*, b. p. 188—190°/6 mm. (90% yield) (Found: Cl, 14·2. $C_{14}H_{12}ONCl$ requires Cl, 14·5%); N-*phenyl*-α-*naphthimidoyl chloride* (81% yield), needles (from benzene), m. p. 95° (Found: Cl, 13·6. $C_{17}H_{12}NCl$ requires Cl, 13·4%); N-*phenyl*-o-*toluimidoyl chloride*, b. p. 174—177°/10 mm. (90% yield) (Found: Cl, 15·3. $C_{14}H_{12}NCl$ requires Cl, 15·45%).

Preparation of N-*Aroyl*-o-*nitrobenzamides*.—The imidoyl chloride (1 mol.) in twice its weight of dry acetone was mixed with sodium *o*-nitrobenzoate (1·1 mol.) in five times its weight of acetone. Precipitation of sodium chloride occurred immediately and after 1 hr. at room temperature the acetone was removed by distillation. The residue was extracted with boiling water to remove sodium chloride and excess of sodium *o*-nitrobenzoate, and the insoluble portion crystallised from an appropriate solvent. Yields of 90—95% (based on imidoyl chloride used) were obtained for the *compounds* listed in Table 1.

Table 1. N-*Aroyl*-o-*nitrobenzamides*, $o\text{-}NO_2\cdot C_6H_4\cdot CO\cdot NAr\cdot COAr'$.

					Found (%):			Rqd. (%):	
Ar	Ar′	M. p.	Form	Solvent	C	H	Formula	C	H
Ph	Ph	173—174° [a]	Needles	Aq. AcOH	69·2	4·0	$C_{20}H_{14}O_5N_2$	69·4	4·05
o-C_6H_4Me	Ph	131—132	Plates	EtOH	70·0	4·5			
m-C_6H_4Me	Ph	141—142	,,	AcOH	69·6	4·3 [b]	$C_{21}H_{16}O_4N_2$	70·0	4·4
p-C_6H_4Me	Ph	175—177	Needles	AcOH	69·9	4·6			
o-C_6H_4·OMe	Ph	122—123	,,	EtOH	66·9	4·2			
p-C_6H_4·OMe	Ph	114—115	,,	EtOH	67·1	4·25	$C_{21}H_{16}O_5N_2$	67·0	4·25
β-$C_{10}H_7$	Ph	176	Plates	AcOH	72·6	4·1			
Ph	α-$C_{10}H_7$	—	Needles	Aq. AcOH	72·5	4·1	$C_{24}H_{16}O_4N_2$	72·7	4·0
2:4-$C_6H_3Me_2$	Ph	113	Plates	EtOH	70·2	4·6	$C_{22}H_{18}O_4N_2$	70·6	4·8
Ph	o-C_6H_4Me	122—123	Needles	EtOH	69·8	4·5	$C_{21}H_{16}O_4N_2$	70·0	4·4
Ph	p-C_6H_4Cl	150—151	Flakes	AcOH	[c]	—	$C_{20}H_{13}O_4N_2Cl$	—	—

[a] Obtained also from *o*-nitrobenzimidoyl chloride and sodium benzoate. [b] Found: N, 7·7. Reqd.: N, 7·8%. [c] Found: Cl, 7·3. Reqd.: Cl, 7·4%.

Preparation of 2:3-*Diaryl*-4-*quinazolones*.—(1) Solutions of the arylimidoyl chloride (1 mol.) and ammonium anthranilate (1·5 mol.) in acetone at room temperature were mixed and after 2 hr. the precipitate of ammonium chloride was filtered off. Water was added to incipient crystallisation, and the mixture set aside for 12 hr. This crystalline deposit (A) was filtered off and washed with acetone. The washings and filtrate, on evaporation, gave further crystals (B). Examination of (A) from condensations of ammonium anthranilate with *N*-phenyl-, *N*-*m*-tolyl-, *N*-*p*-methoxyphenyl-, and *N*-β-naphthyl-benzimidoyl chloride proved that (A) was in each case an *o*-aroylamino-*N*-arylbenzamide, which when heated above the m. p. gave the corresponding 2:3-diaryl-4-quinazolone. For comparison the *o*-arylamino-*N*-arylbenzamides were prepared in good yields from benzcylanthranil (1 mol.) and the appropriate primary aromatic amine (1 mol.) either by heating them [3a] at 180° or by refluxing them in acetone for 1 hr., water being then added dropwise to the boiling solution until a precipitate formed. After cooling, the precipitate was filtered off and crystallised.

o-Benzamidobenzanilide crystallises from ethyl benzoate in needles, m. p. 277° (Found: C, 75·8; H, 5·0. Calc. for $C_{20}H_{16}O_2N_2$: C, 75·9; H, 5·1%), *o*-benzamidobenzo-*m*-toluidide from acetic acid in needles, m. p. 224° (Found: C, 76·1; H, 5·6. Calc. for $C_{21}H_{18}O_2N_2$: C, 76·3; H, 5·5%), *o*-*benzamidobenzo*-p-*anisidide* from chlorobenzene in needles, m. p. 228° (Found: C, 73·0; H, 5·1. $C_{21}H_{18}O_3N_2$ requires C, 72·8; H, 5·2%), and *o*-benzamidobenzo-β-naphthalide from ethyl benzoate in needles, m. p. 258° (lit.,[5] 258°).

Benzoylanthranil was obtained by heating a mixture of anthranilic acid (25 g.) with benzoyl chloride (60 g.) at 150° for 1½ hr. After removal of benzoic acid and excess of benzoyl chloride at 5 mm., the residue of benzoylanthranil [3a] was crystallised from acetic anhydride (28 g.; m. p. 123°). It was also prepared by treating benzoylanthranilic acid (10 g., 1 mol.) with a large excess (20 g.) of thionyl chloride: when reaction had ceased, the excess of thionyl chloride was removed and the residual benzoylanthranil distilled at 189—192°/8 mm. (yield 9·5 g., 97%; m. p. 123°).

Crystals (B) were basic and readily soluble in 2N-hydrochloric acid, and after filtration of the

[3] Wallach, *Annalen*, 1877, **184**, 1.
[4] Von Braun and Pinkernelle, *Ber.*, 1934, **67**, 1218.
[5] de Diesbach, Jacobi, and Taddei, *Helv. Chim. Acta*, 1942, **23**, 469.

acidic solution addition of aqueous ammonia gave a copious precipitate of 2 : 3-diaryl-4-quinazolone.

An alternative procedure, which eliminated the formation of *o*-aroylamino-*N*-arylbenzamides and gave good yields of the quinazolones, was to add, for example, finely powdered ammonium anthranilate (1·7 g., 1·1 mol.) to a solution of *N*-phenylbenzimidoyl chloride (2·15 g., 1 mol.) in acetone (15 c.c.) with shaking. After 1 hr. at room temp. the solution was poured into cold water (500 c.c.), and the precipitated base filtered off. Two crystallisations from dilute alcohol gave 2 : 3-diphenyl-4-quinazolone (70%, 2 g.), m. p. and mixed m. p. 158—159°.

(2) The arylimidoyl chloride (1 mol.), dissolved in approx. twice its weight of dry acetone, was added slowly with shaking to a solution of methyl anthranilate (2 mol.) in ten times its volume of acetone at 0°. After 12 hr. at room temperature the acetone was removed and the gummy residue extracted with warm concentrated hydrochloric acid, then filtered off, and the filtrate was poured into a large excess of cold concentrated aqueous ammonia. Unchanged methyl anthranilate was removed in a current of steam, and the residue filtered off and crystallised. The yields of 2 : 3-diaryl-4-quinazolones varied from 75 to 85%.

TABLE 2. *2 : 3-Disubstituted quinazolones.*

2-Subst.	3-Subst.	Method (yield)	M. p.	Form	Solvent	Found (%): C	H	Formula	Reqd. (%): C	H
Ph [a]	Ph	1, 2, 3	158°	Needles	EtOH	—		—	—	—
Ph	*o*-C_6H_4Me	3 (75%)	142—143	Plates	Aq. EtOH	80·8	5·1 [b]	$C_{21}H_{16}ON_2$	80·7	5·2
Ph [c]	*m*-C_6H_4Me	1, 2, 3 (80%)	144—145	Needles	Aq. EtOH	80·55	5·3			
Ph	*p*-C_6H_4Me	3 (90%)	180—181	Plates	EtOH	80·7	5·05 [d]			
Ph	*o*-C_6H_4·OMe	2, 3 (80%)	159—160	Needles	Aq. EtOH	76·8	5·0 [e]	$C_{21}H_{16}O_2N_2$	76·8	4·9
Ph	*p*-C_6H_4·OMe	1, 2, 3 (90%)	197	Leaflets	EtOH	76·8	4·9			
Ph	β-$C_{10}H_7$	"	182—183	Needles	Aq. EtOH	82·6	4·6	$C_{24}H_{16}ON_2$	82·8	4·6
Ph [f]	2 : 4-$C_6H_3Me_2$	2, 3 (75%)	135—136	Plates	—	80·9	5·4 [g]	$C_{23}H_{18}ON_2$	81·0	5·5
p-C_6H_4Cl	Ph	2, 3 (80%)	175—176	Needles	Aq. EtOH		[h]	$C_{20}H_{13}ON_2Cl$	—	—
o-C_6H_4Me	Ph	3 (80%)	152	Plates	EtOH	80·6	5·2 [i]	$C_{21}H_{16}ON_2$	80·7	6·2
α-$C_{10}H_7$	Ph	2, 3 (90%)	180	Prisms	Aq. EtOH	82·5	4·3	$C_{24}H_{16}ON_2$	82·8	4·6

[a] Hirwe and Kulkarni [6] give m. p. 186°. Mumm *et al.*[1] and de Diesbach *et al.*[5] give 158°. [b] Found: N, 9·1. Reqd.: N, 9·0%. [c] Hirwe *et al.*[6] give m. p. 145°, de Diesbach *et al.*[5] give 139°. [d] Found: N, 9·0. Reqd.: N, 9·0%. [e] Found: N, 8·8. Reqd.: N, 8·5%. [f] de Diesbach *et al.*[5] give m. p. 130°. [g] Found: N, 8·4. Reqd.: N, 8·6%. [h] Found: N, 8·4. Calc.: N, 8·6%. [i] Found: N, 8·8. Reqd.: N, 9·0%.

(3) Sodium dithionite (hydrosulphite) (10 mol.) in the minimum volume of cold water was added dropwise to a boiling ethanolic solution of the nitro-compound (1 mol.). Any material which separated was brought into solution by addition of solvent. The alcohol was removed by distillation and the residual liquid poured into a large volume of cold water. The precipitated material was filtered off, washed repeatedly with boiling water to remove inorganic matter and extracted with warm concentrated hydrochloric acid to dissolve the quinazolone. An insoluble residue of unchanged nitro-compound was filtered off, the filtrate poured into a large excess of aqueous ammonia, and the precipitated base crystallised. The yields of quinazolones were of the order of 90% after allowance for the nitro-compound recovered. Attempts to reduce the nitro-compounds with tin and hydrochloric acid gave small yields (15%) of quinazolones; better yields (40%) were obtained by using alcohol to dissolve the nitro-compound. Quinazolones prepared are reported in Table 2.

3-m-*Nitrophenyl*-2-*phenyl*-4-*quinazolone*. The best yield (60%) was obtained by heating a mixture of *m*-nitroaniline (2·8 g., 1 mol.) and benzoylanthranil (4·5 g., 1 mol.) at 300° for 1 hr. After cooling, the melt was extracted with acetic acid (50%) (charcoal); the solution deposited yellow needles of the *quinazolone*, m. p. 199° (Found: C, 70·1; H, 3·8; N, 12·2. $C_{20}H_{13}O_3N_3$ requires C, 70·0; H, 3·8; N, 12·25%). Methods 1 and 2 gave 15% yields.

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[6] Hirwe and Kulkarni, *Proc. Indian Acad. Sci.*, 1942, **16**, *A*, 296.

206. *Plant Gums of the Genus* Khaya. *The Structure of* Khaya grandifolia *Gum.*

By G. O. Aspinall, E. L. Hirst, and N. K. Matheson.

Khaya grandifolia gum has been shown to be composed of residues of D-galactose, L-rhamnose, D-galacturonic acid, and 4-*O*-methyl-D-glucuronic acid, with traces of L-arabinose. Hydrolysis of the methylated gum indicated the presence therein of residues of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose, 2 : 3 : 6-tri-*O*-methyl-D-galactose, 3-*O*-methyl-L-rhamnose, 2 : 3 : 4-tri-*O*-methyl-D-glucuronic acid and 2 : 3-di-*O*-methyl-D-galacturonic acid. On partial hydrolysis the gum gave two aldobiouronic acids, 2-*O*-D-galacturonosyl-L-rhamnose and 4-*O*-(4-*O*-methyl-D-glucuronosyl)-D-galactose, an aldotriouronic acid, *O*-D-galacturonosyl-(1→2)-*O*-L-rhamnose-(1→4)-D-galactose, and other acidic oligosaccharides.

Khaya senegalensis gum has been shown to be composed of the same sugar residues, but in different proportions.

The gum exudate of *Khaya grandifolia*, the West African mahogany tree, has been examined by McIlroy,[1] who obtained evidence for the presence of residues of galactose, rhamnose, and galacturonic acid. The gum, therefore, appeared to be similar to the gums of *Sterculia setigera* [2] and *Cochlospermum gossypium* (" Karaya " gum) [3] rather than to the glucuronic acid-containing gums of the *Acacia* [4-6] and *Prunus* [7-9] genera. A quantity of the gum was kindly placed at our disposal by Dr. R. J. McIlroy and in the present study the main structural features of the gum have been investigated.

The gum we examined had been purified by dissolution in 4% sodium hydroxide solution, and was further purified by precipitation from acid solution with acetone and then by re-precipitation from aqueous solution with ethanol. The purified gum, in contrast with the crude material, was readily soluble in water. It is possible that the treatment with alkali had removed ester groupings as several plant gums [2,3] are known to occur as partly acetylated polysaccharides. The gum had a uronic anhydride content [10] of 47% (calculated for a substance of equivalent weight 344, 51%) and a low, but significant, methoxyl content (1%).

The gum was extremely resistant to hydrolysis, and even after hydrolysis with 2N-sulphuric acid for 18 hr. at 100° the yield of neutral sugars was low, quantitative estimation [11] indicating the presence of galactose (18%), rhamnose (15%), and arabinose (1%) (results expressed as percentages of anhydro-sugar originally present in the gum). After hydrolysis of the gum with N-sulphuric acid at 100° for 6 hr. L-rhamnose (3·7%), L-arabinose (0·2%), and D-galactose (18·0%) were isolated as crystalline compounds. The incompletely hydrolysed acidic residue (52% of the original weight of gum) was converted into the methyl ester methyl glycoside, reduced with potassium borohydride, and rehydrolysed, the following sugars being then identified : L-rhamnose (10·1%), 4-*O*-methyl-D-glucose (2·0%), D-glucose (trace), and D-galactose (26·6%). It is probable that the trace of glucose arose from the demethylation of 4-*O*-methyl-D-glucose during the hydrolysis. As 4-*O*-methyl-D-glucose was not found in the hydrolysate of the gum before treatment of the gum with potassium borohydride, it must have been formed by the reduction of

[1] McIlroy, *J.*, 1952, 1918.
[2] Hirst, Hough, and Jones, *J.*, 1949, 3145; Hough and Jones, *J.*, 1950, 1199.
[3] Hirst and Dunstan, *J.*, 1953, 2332.
[4] Challinor, Haworth, and Hirst, *J.*, 1931, 258; Smith, *J.*, 1939, 744, 1724; Jackson and Smith, *J.*, 1940, 74, 79.
[5] Stephen, *J.*, 1951, 646; Hirst and Perlin, *J.*, 1945, 2622; Charlson, Nunn, and Stephen, *J.*, 1955, 269.
[6] Charlson, Nunn, and Stephen, *J.*, 1955, 1428.
[7] Hirst and Jones, *J.*, 1938, 1174; 1939, 1482; 1946, 506.
[8] Jones, *J.*, 1939, 558; 1947, 1055; 1949, 3141.
[9] Hirst and Jones, *J.*, 1947, 1064; 1948, 120; Brown, Hirst, and Jones, *J.*, 1949, 1757.
[10] McCready, Swenson, and Maclay, *Ind. Eng. Chem. Anal.*, 1946, **18**, 290.
[11] Hirst and Jones, *J.*, 1949, 1659.

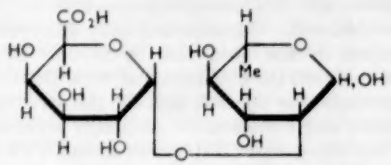
4-*O*-methyl-D-glucuronic acid residues. The combined yield of L-rhamnose and D-galactose (58·4%) was greater than could be derived from neutral sugar residues in a gum containing 47% of uronic anhydride, therefore some of the D-galactose could only have arisen from the reduction of D-galacturonic acid residues in the original gum. Further evidence for the presence of galacturonic residues was obtained on nitric acid oxidation of the gum; the yield of mucic acid indicated the presence in the gum of 58% of galactose and/or galacturonic acid residues.

The methylated gum was prepared in the usual way and like the parent gum was extremely resistant to hydrolysis. The hydrolysate was fractionated chromatographically on cellulose,[12] giving 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose, 2 : 3 : 6-tri-*O*-methyl-D-galactose, and 3-*O*-methyl-L-rhamnose (all identified as crystalline derivatives), a trace of an unidentified di-*O*-methylgalactose (probably of no structural significance), and a mixture of acidic substances. After attempts to separate the acidic components had failed, the acids were converted into the methyl ester methyl glycosides, which were reduced with lithium aluminium hydride. The reduced glycosides were hydrolysed and the resulting neutral sugars were partitioned on cellulose. Further quantities of 2 : 3 : 6-tri-*O*-methyl-D-galactose and 3-*O*-methyl-L-rhamnose were isolated, and in addition 2 : 3 : 4-tri-*O*-methyl-D-glucose and 2 : 3-di-*O*-methyl-D-galactose were characterised by the formation of crystalline derivatives. As the last two sugars were not present amongst the neutral sugars isolated on direct hydrolysis of the methylated gum it is clear that they were formed by the reduction of 2 : 3 : 4-tri-*O*-methyl-D-glucuronic and 2 : 3-di-*O*-methyl-D-galacturonic acids respectively. No methyl ethers of L-arabinose were detected.

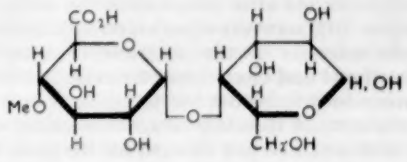
The mixture of acidic substances obtained on partial hydrolysis of the gum was fractionated by stepwise elution from a column of an anion-exchange resin [13] with increasing concentrations of acetic acid, to give a hexuronic acid, a mixture of aldobiouronic acids, an aldotriouronic acid, and other incompletely identified acidic oligosaccharides. The hexuronic acid, isolated in 1·3% yield from the gum, was identified as galacturonic acid by bromine oxidation to mucic acid. The aldobiouronic acid fraction, isolated in 10% yield, was shown by paper ionophoresis [14] to contain two components with slightly different M_G values, although the two substances travelled at the same rate on a paper chromatogram. Hydrolysis of the mixture of acids gave rhamnose, galactose, galacturonic acid, and 4-*O*-methylglucuronic acid, but, after oxidation of the disaccharides with bromine water, rhamnose and galactose could no longer be detected on hydrolysis. The aldobiouronic acids were converted into a mixture of fully methylated disaccharides by reduction of the acidic residues in the methylated aldobiouronic acids with lithium aluminium hydride followed by further methylation of the reduction products. Hydrolysis of the methylated disaccharides then yielded the following sugars, which were identified as crystalline derivatives: 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose, 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose, 3 : 4-di-*O*-methyl-L-rhamnose, and 2 : 3 : 6-tri-*O*-methyl-D-galactose. Although these results indicate the mode of linkage of the sugar residues in the aldobiouronic acids, they do not provide evidence for the combination of sugars. Two observations, however, point to 2-*O*-D-galacturonosyl-L-rhamnose (I) and 4-*O*-(4-*O*-methyl-D-glucuronosyl)-D-galactose (II) as structures of the aldobiouronic acids. First, the two aldobiouronic acids travel on the chromatogram at the same rate, whereas it would be expected from the known rates of movement of the constituent sugars that aldobiouronic acids, in which the sugars were linked in the alternative manner, would travel at different rates. Secondly, only a small difference in the ionophoretic mobilities of the aldobiouronic acids (I) and (II) would be expected, as each disaccharide contains one pair of hydroxyl groups [the 3 : 4-hydroxyl groups of the galacturonosyl residue in (I) and the 1 : 2-hydroxyl groups of the galactose residue in (II)] capable of complex formation with boric acid and the carboxyl group of the acidic residue. On the other hand, the alternative pair of aldobiouronic acids, 4-*O*-D-galacturonosyl-D-galactose and 2-*O*-(4-*O*-methyl-D-glucuronosyl)-L-rhamnose, would be

[12] Hough, Jones, and Wadman, *J.*, 1949, 2511.
[13] Weissman, Meyer, Sampson, and Linker, *J. Biol. Chem.*, 1954, **208**, 417; Derungs and Deuel, *Helv. Chim. Acta*, 1954, **37**, 657.
[14] Consden and Stanier, *Nature*, 1952, **169**, 783.

expected to show greatly different ionophoretic mobilities [15] as the former compound would contain two pairs of hydroxyl groups capable of complex formation with boric acid, whereas the latter would contain none. These two aldobiouronic acids have been previously isolated from the hydrolysis of plant gums, namely, 2-*O*-D-galacturonosyl-L-rhamnose from *Sterculia setigera* [2] and *Cochlospermum gossypium* [3] gums, and 4-*O*-(4-*O*-methyl-D-glucuronosyl)-D-galactose from gum myrrh.[16]



(I)



(II)

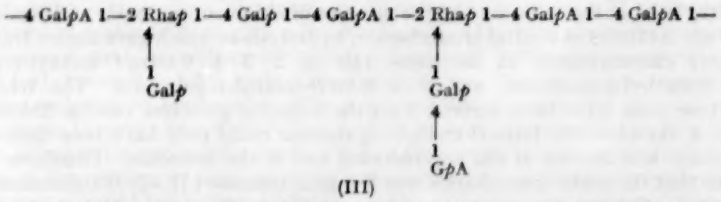
An aldotriouronic acid (equivalent weight 490) was isolated in 7·0% yield, and gave on hydrolysis galactose and rhamnose. After oxidation of the trisaccharide with bromine water only rhamnose was detected on hydrolysis, and after reduction of the acidic residue with potassium borohydride and hydrolysis the products were galactose and rhamnose. The acidic trisaccharide, therefore, contained residues of galactose, rhamnose, and galacturonic acid, the galactose residue forming the reducing group. The aldotriouronic acid was methylated in the same way as the mixture of aldobiouronic acids and was converted into a fully methylated neutral trisaccharide, hydrolysis of which gave sugars travelling on the paper chromatogram at the same rate as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose, 3 : 4-di-*O*-methyl-L-rhamnose, and 2 : 3 : 6-tri-*O*-methyl-D-galactose. The tri-*O*-methyl-D-galactose must have been derived from the reducing galactose residue linked through position 4, therefore the tetra-*O*-methyl-D-galactose could only have been formed from a galacturonic acid residue at the non-reducing end of the molecule. It follows from this evidence that the acidic trisaccharide was *O*-D-galacturonosyl-(1→2)-*O*-L-rhamnosyl-(1→4)-D-galactose. Other acidic oligosaccharides were obtained in low yield, but although these were all shown to be composed of galactose, rhamnose, and galacturonic acid residues, insufficient quantities were isolated for detailed structural studies. The high proportion of acid residues in one of these fractions (equivalent weight 300) suggested that the gum may contain adjacent galacturonic residues.

The main structural features of *K. grandifolia* gum are now clear from this investigation. From the methylation studies it is evident that end-groups of D-galactose and 4-*O*-methyl-D-glucuronic acid occur in the gum whilst L-rhamnose residues provide the only branching points in the molecule and 1 : 4-linked D-galacturonic acid residues occur in the main chains. The evidence for the presence of the aldobiouronic acid 2-*O*-D-galacturonosyl-L-rhamnose (I) in the products of partial hydrolysis shows that the L-rhamnose residues are linked through positions 1 and 2 in the main chain and that the side chains must be linked through position 4. As glycosiduronic acid linkages are particularly resistant to acid hydrolysis, the evidence that on mild acid hydrolysis of the gum only galactose, together with small amounts of arabinose, was formed and no significant amounts of neutral disaccharides were detected, suggests that the D-galactose end-groups are linked directly to the L-rhamnose residues. On the other hand, the identification of the aldobiouronic acid 4-*O*-(4-*O*-methyl-D-glucuronosyl)-D-galactose (II) on partial acid hydrolysis of the gum shows that the 4-*O*-methyl-D-glucuronic acid end-groups are linked to the main chain through 1 : 4-linked D-galactose residues in two-residue side-chains. The isolation of the aldotriouronic acid, *O*-D-galacturonosyl-(1→2)-*O*-L-rhamnosyl(1→4)-D-galactose, shows that some 1 : 4-linked D-galactose residues are also present in the main chain. In addition, the main chain

[15] Foster, *J.*, 1953, 982; Foster and Stacey, *J.*, 1955, 1778.
[16] Jones and Nunn, *J.*, 1955, 3001.

probably contains adjacent D-galacturonic acid residues, as indicated by the oligosaccharides of high uronic acid content isolated on partial acid hydrolysis of the gum; indeed, the high uronic acid content of the gum itself can only be explained on this basis.

Throughout this investigation the hydrolyses of both the original gum and its methyl ether were accompanied by considerable decomposition and the yields of sugars isolated were low. An attempt to obtain a quantitative estimate of the ratio of methylated sugar residues present in the methylated gum was made by hydrolysing samples of the methylated polysaccharide after reduction of the acidic residues with lithium aluminium hydride, but only an 80% recovery of sugars on hydrolysis was obtained. Consequently only an approximate estimate of the constituent sugars present in the gum can be made. Ultracentrifugal and electrophoretic examinations of the gum (in collaboration with Dr. C. T. Greenwood) indicated the presence of only one molecular species, and all the structural features must therefore be accommodated within a single molecule. Although no unique structure can be put forward for the gum, the repeating unit (III) shown includes all the known types of linkage present in the gum, and the ratio of constituent sugar residues, namely, D-galactose (3 parts), L-rhamnose (2 parts), D-galacturonic acid (4 parts) and 4-*O*-methyl-D-glucuronic acid (1 part), is consistent with the quantitative measurements made, when allowance is made for the decomposition of sugars during hydrolysis. The ultracentrifugal studies indicated that the gum was of high molecular weight although no accurate value is yet available, and the end-groups of D-galactose and 4-*O*-methyl-D-glucuronic acid must therefore occur in the side-chains rather than as the non-reducing terminal residues of the backbone of the molecule.



(III)

(Gal *p*A = D-galactopyranuronic acid, Gal*p* = D-galactopyranose, Rha*p* = L-rhamnopyranose, and *Gp*A = 4-*O*-methyl-D-glucopyranuronic acid.)

These results show that *Khaya grandifolia* gum contains several interesting structural features. The occurrence of two different uronic acid residues within a single molecule is a unique feature of the plant gums so far examined. On previous occasions when two aldobiouronic acids have been isolated from the partial hydrolysis of a plant gum, these have contained the same uronic acid residue linked either to different sugars or to the same sugar through different positions. The gum resembles in some respects those from *Sterculia setigera* [2] and *Cochlospermum gossypium*,[3] which also contain D-galactose, L-rhamnose, and D-galacturonic acid residues, although the present gum contains in addition 4-*O*-methyl-D-glucuronic acid residues. As is also the case for these gums the D-galactose residues in *K. grandifolia* gum are linked through positions 1 and 4, in contrast with damson,[7] cherry,[8] and egg-plum [9] gums, and the gums of the *Acacia* group [5, 6] where the D-galactose residues are linked through positions 1 and 3, and 1 and 6. *K. grandifolia* gum, however, differs from *S. setigera* and *C. gossypium* gums in that L-rhamnose occurs solely as branching points in the central part of the molecular structure and is not also found linked through positions 1 and 2 only. The gum differs also from *S. setigera* gum in that the D-galacturonic acid residues are linked only through positions 1 and 4 in the main chain and do not form the branching points of the gum molecule.

Recent investigations of the gums of the *Acacia* genus [5, 6] have shown that different gums contain the same constituent sugars and in each case the aldobiouronic acid, 6-*O*-D-glucuronosyl-D-galctose, has been isolated from the products of partial hydrolysis, but the proportions in which the sugar residues are present differ markedly. It was of interest therefore to examine another gum of the *Khaya* genus. *Khaya senegalensis* gum was

obtained in the natural state as a partially acetylated polysaccharide, and was purified by dissolution in aqueous sodium hydroxide and isolated as a white amorphous powder after three reprecipitations from aqueous solution with ethanol. The purified gum had an equivalent weight of 412 and a methoxyl content of 1·2%. After partial hydrolysis, L-rhamnose (4·0%), L-arabinose (2·1%), and D-galactose (16·1%) were isolated as crystalline compounds. The incompletely hydrolysed acidic residue (37·8%), which had an equivalent weight of 348, liberated further quantities of rhamnose and galactose on extended hydrolysis. Chromatographic examination of the acidic residue indicated a mixture of acidic oligosaccharides similar to that obtained on partial hydrolysis of *K. grandifolia* gum. After conversion into the methyl ester methyl glycoside, reduction with potassium borohydride, and hydrolysis of the reduction product, chromatographic examination of the hydrolysate showed rhamnose, 4-*O*-methylglucose, glucose (trace), and galactose to be present. The methoxyl content of the gum was not high enough for all the uronic acid to be present as 4-*O*-methylglucuronic acid, so it is probable that galacturonic acid is also a constituent sugar of the gum. *K. senegalensis* gum, therefore, contains the same sugar residues as *K. grandifolia* gum, but the proportions of uronic acid and L-arabinose are different. The evidence at present available indicates that in the *Khaya* genus the position in regard to the composition of the various gums is similar to that found for *Acacia* species.

Experimental

Paper partition chromatography was carried out on Whatman No. 1 filter paper, with the upper layers of the following solvent systems (v/v): (*A*) butan-1-ol–benzene–pyridine–water (5 : 1 : 3 : 3); (*B*) butan-1-ol–ethanol–water (4 : 1 : 5); (*C*) butan-1-ol–acetic acid–water (4 : 1 : 5); (*D*) butal-1-ol–acetic acid–water (8 : 2 : 5); (*E*) benzene–ethanol–water (169 : 47 : 15). Paper ionophoresis [14] was carried out in borate buffer at pH 10.

Purification and Properties of Khaya grandifolia *Gum.*—The gum was received from Dr. R. J. McIlroy as a light grey powder which had been reprecipitated with ethanol after dissolution in 4% aqueous sodium hydroxide.[1] The gum acid was precipitated from solution in dilute hydrochloric acid with ethanol and reprecipitated from aqueous solution with acetone, to give a white amorphous powder, $[\alpha]_D^{18}$ +122° (unchanged on further reprecipitation) (*c*, 1·88 in H_2O) [Found: equiv., 344 (by titration); uronic anhydride, 47·2% (by decarboxylation); ash, nil; OMe, 1·0%].

Chromatographic examination of the hydrolysate of the gum after it had been heated with N-sulphuric acid at 100° showed that galactose and arabinose (trace) were released after 0·5 hr. and that rhamnose appeared after 3 hr. The hydrolysis of the gum under milder conditions was also followed (autohydrolysis at 100° for 40 hr., hydrolysis with 0·01N-sulphuric acid at 100° for 40 hr., and hydrolysis with 0·1N-sulphuric acid at 100° for 14 hr.), but in no case were significant amounts of neutral disaccharides detected in addition to galactose and arabinose.

Quantitative estimation, by the method of Hirst and Jones,[11] of the sugars produced on hydrolysis of the gum with N-sulphuric acid at 100° for 6 hr. indicated the presence of the following sugars (calc. as percentage of anhydro-sugar in the original gum): galactose, 16·1; rhamnose, 8·2; arabinose, <1%. After hydrolysis of the gum with 2N-sulphuric acid at 100° for 18 hr. the same sugars were present in the following quantities: galactose, 18·0; rhamnose, 14·7; arabinose, <1%. Oxidation of the gum with nitric acid and estimation of the mucic acid (m. p. and mixed m. p. 216°) formed indicated the presence in the gum of 58% of galactose and/or galacturonic acid residues.

Partial Hydrolysis of the Gum.—The purified gum (10 g.) was heated with N-sulphuric acid (250 c.c.) at 100° for 6 hr., the hydrolysate was neutralised with barium hydroxide, the excess of alkali rapidly destroyed with carbon dioxide, and the filtrate was taken to dryness. The residue was fractionated on cellulose,[12] with butan-1-ol saturated with water plus 10% of ethanol, as the eluant, giving four fractions.

Fraction 1 (0·370 g.) had $[\alpha]_D^{17}$ +9·8° (equil.) (*c*, 4·44 in H_2O) and after recrystallisation from ethanol had m. p. and mixed m. p. (with L-rhamnose hydrate) 95°. Fraction 2 (0·023 g.) had $[\alpha]_D^{17}$ +104° (equil.) and after recrystallisation from methanol had m. p. and mixed m. p. (with L-arabinose) 155°. Fraction 3 (1·80 g.) had $[\alpha]_D^{16}$ +81° (equil.) and after recrystallisation from methanol had m. p. and mixed m. p. (with D-galactose) 164°. Fraction 4, obtained by elution

of the cellulose with water, consisted of the barium salts of acidic material (Found : Ba, 17·4%). Barium ions were removed by passage through a column of Amberlite resin IR-120(H) and the solution was freeze-dried to give the acidic fraction (A) (5·2 g.) which was examined later.

Hydrolysis of the Acidic Fraction (A) after Reduction with Potassium Borohydride.—The acidic fraction (A) (4·5 g.) was set aside overnight in methanolic 4% hydrogen chloride and then refluxed for 7 hr. After neutralisation with silver carbonate, the dry residue was dissolved in water (100 c.c.) and the solution was added slowly to a solution of potassium borohydride (2·3 g.) in water (100 c.c.). After 2 hr., the excess of borohydride was destroyed by the addition of dilute acetic acid, and the solution was de-ionised by passage through columns of Amberlite resins IR-120 and IR-4*B*. After being taken to dryness the residue was hydrolysed by N-sulphuric acid at 100° for 18 hr. Chromatographic examination of the hydrolysate showed rhamnose, 4-*O*-methylglucose, glucose (trace), and galactose, and partition on cellulose, with, as eluant, butan-1-ol saturated with water, gave pure fractions of glucose and galactose, and a mixture of rhamnose and 4-*O*-methylglucose. Most of the rhamnose crystallised on trituration of the mixed fraction with moist butan-1-ol and complete separation of the two components was achieved by further partition on cellulose. Examination of the four fractions confirmed the identity of the sugars. Fraction 1 (0·878 g.) had $[\alpha]_D^{18}$ +10° (equil.) (*c*, 2·35 in H_2O) and after recrystallisation from moist butan-1-ol had m. p. and mixed m. p. (with L-rhamnose hydrate) 95°. Fraction 2 (0·173 g.) had $[\alpha]_D^{20}$ +62° (Found : OMe, 15·5. Calc. for $C_7H_{14}O_6$: OMe, 15·9%), and was identified as 4-*O*-methyl-D-glucose by conversion into the osazone, m. p. 154°, $[\alpha]_D^{19}$ −31°→−14° (equil.) (*c*, 1·11 in H_2O). Fraction 3 (11 mg.) travelled on the chromatogram at the same rate as D-glucose and was destroyed on incubation with glucose-oxidase. Fraction 4 (2·30 g.) had $[\alpha]_D^{18}$ +81° (equil.) (*c*, 2·34 in H_2O) and after recrystallisation from methanol had m. p. and mixed m. p. (with D-galactose) 163°.

Separation of Acidic Components obtained on Partial Hydrolysis of the Gum.—The acidic fraction (A) (4·0 g.) was absorbed on a column of Amberlite resin IRA-400 (acetate form) (30 × 3·4 cm.; 100 mesh) and the column was eluted with increasing concentrations of dilute acetic acid (0·1—1·0 by stages of 0·1%, 1·0—2·0 by 0·2%, 2·0—5·0 by 0·5%, and 5·0—15·0 by 2·5%). Six main fractions were obtained together with small quantities of complex mixtures which were not examined further.

Fraction 1. The syrup (0·172 g., eluted with 0·2—0·7% acetic acid) contained a main component having R_{Gal} 0·40 (rate of movement relative to galactose in solvent *D*) and M_G 0·65 (rate of movement on the ionophoretogram relative to glucose). Hydrolysis with 2N-sulphuric acid at 100° for 18 hr. gave galactose and rhamnose, but after oxidation with bromine water hydrolysis gave galactose and only a trace of rhamnose. Hydrolysis of the syrup after reduction of the methyl ester methyl glycoside with potassium borohydride gave galactose and rhamnose.

Fraction 2. The syrup (0·731 g., eluted with 0·8—1·0% acetic acid) had $[\alpha]_D^{16}$ +130° (*c*, 1·83 in H_2O). Chromatographic examination suggested the presence of two components, R_{Gal} 0·80, which were incompletely resolved, but complete resolution was achieved on the ionophoretogram (M_G 0·82 and 0·69). Hydrolysis with 2N-sulphuric acid gave rhamnose, galactose, galacturonic acid, and 4-*O*-methylglucuronic acid, but after oxidation with bromine water hydrolysis gave the acidic components only.

A portion of the syrup (0·60 g.) was methylated four times with methyl sulphate and sodium hydroxide, and the product (after extraction of the acidified reaction mixture with chloroform) (0·684 g.) was further methylated with methyl iodide and silver oxide. After removal of the solvent, the syrup was dissolved in dry tetrahydrofuran and added slowly to lithium aluminium hydride (0·30 g.) in tetrahydrofuran. After 3 hr. the excess of lithium aluminium hydride was destroyed by the addition of water, and the solution was acidified and extracted with chloroform. The extract was re-methylated three times with methyl iodide and silver oxide, and the mixture of methylated disaccharides was isolated as a yellow syrup (0·410 g.) (Found : OMe, 52·1. A methylated disaccharide composed of a hexose and a deoxyhexose residue requires OMe, 51·1%, and a methylated disaccharide composed of two hexose residues requires OMe, 54·6%). The methylated sugars were hydrolysed with N-sulphuric acid (10 c.c.) at 100° for 16 hr. and the hydrolysate was separated on cellulose, with light petroleum (b. p. 100—120°)–butan-1-ol (7 : 3), saturated with water, as eluant, to give three fractions. Fraction *a* (93 mg.) crystallised and had m. p. and mixed m. p. (with 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose) 84°, $[\alpha]_D^{17}$ +82° (equil.) (*c*, 1·12 in H_2O) (Found : OMe, 52·8. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). Fraction *b* (200 mg.) contained two sugars having R_G 0·88 and 0·84 in solvent *B*, which were separated on filter sheets with solvent *E* to give fractions *b*(i) (82 mg.) and *b*(ii) (76 mg.). Fraction *b*(i) had $[\alpha]_D^{18}$ +97° (equil.) (*c*, 1·32 in H_2O) and was identified as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose

by conversion into the aniline derivative, m. p. and mixed m. p. 194°, $[\alpha]_D^{18}$ −60°→+18° (equil.) (*c*, 0·8 in Me_2CO). Fraction *b*(ii) had $[\alpha]_D^{17}$ +20° (equil.) (*c*, 1·42 in H_2O) (Found: OMe, 32·2. Calc. for $C_8H_{16}O_5$: OMe, 32·3%) and was identified as 3 : 4-di-*O*-methyl-L-rhamnose by conversion into 3 : 4-di-*O*-methyl-L-rhamnono-1 : 5-lactone, m. p. 80°. Fraction *c* (73 mg.) had $[\alpha]_D^{18}$ +88 (equil.) (*c*, 0·5 in H_2O) (Found: OMe, 41·0. Calc. for $C_9H_{18}O_6$: OMe, 41·9%) and was identified as 2 : 3 : 6-tri-*O*-methyl-D-galactose by conversion into 2 : 3 : 6-tri-*O*-methyl-D-galactono-1 : 4-lactone, m. p. and mixed m. p. 96°, $[\alpha]_D^{20}$ −42°→−25° (equil.) (*c*, 0·57 in H_2O).

Fraction 3. The syrup (60 mg., eluted with 1·0—2·0% acetic acid) had R_{Gal} 0·38 and M_G 1·06. Hydrolysis with 2N-sulphuric acid gave rhamnose and galactose, but after oxidation with bromine water hydrolysis gave only rhamnose. Hydrolysis of the syrup after reduction of the methyl ester methyl glycoside with potassium borohydride gave galactose and rhamnose.

Fraction 4. The syrup (0·102 g., eluted with 2·5—3·0% acetic acid) had $[\alpha]_D^{18}$ +30° (*c*, 1·42 in H_2O) and contained a main component, R_{Gal} 0·85 and M_G 1·07, which was identified as D-galacturonic acid by conversion into mucic acid, m. p. and mixed m. p. 220° (decomp.).

Fraction 5. The syrup (0·528 g., eluted with 4·0—12·5% acetic acid) had R_{Gal} 0·36 and M_G 0·79 (Found: equiv., 490). Hydrolysis with 2N-sulphuric acid gave rhamnose and galactose, but after oxidation with bromine water hydrolysis gave only rhamnose. Hydrolysis of the syrup after reduction of the methyl ester methyl glycoside with potassium borohydride gave galactose and rhamnose. A portion of the syrup (0·346 g.) was methylated in the same way as fraction 2 and after reduction of the acidic residues was converted into the fully methylated trisaccharide (0·071 g.). Chromatographic examination of the hydrolysate after it had been heated with N-hydrochloric acid at 100° for 4 hr. showed the presence of sugars travelling at the same rate as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose, 3 : 4-di-*O*-methyl-L-rhamnose, and 2 : 3 : 6-tri-*O*-methyl-D-galactose in solvents *B* and *E*.

Fraction 6. The syrup (0·65 g., eluted with 12·5—15·0% acetic acid) contained a mixture of substances of R_{Gal} 0·0—0·19 with a main component having M_G 0·93 (Found: equiv., 300). Hydrolysis with 2N-sulphuric acid gave galactose and rhamnose, and the same sugars only were formed on hydrolysis after reduction of the methyl ester methyl glycoside with potassium borohydride.

Methylation of the Gum.—The purified gum (20 g.) was methylated six times with methyl sulphate and sodium hydroxide and, after careful acidification of the reaction mixture and dialysis to remove inorganic ions, the partially methylated gum was converted into the silver salt by treatment of an aqueous solution with silver carbonate and the silver salt was isolated by freeze-drying. The silver salt was suspended in a boiling mixture of methyl iodide (80 c.c.) and methanol (100 c.c.), and silver oxide (15 g.) was added during 2 hr. After removal of insoluble silver salts five further methylations were carried out with methyl iodide and silver oxide, the methylated polysaccharide (10·1 g.), soluble in chloroform–light petroleum (b. p. 60—80°) (1 : 4), was isolated having $[\alpha]_D^{16}$ +53° (*c*, 1·32 in $CHCl_3$) (Found: OMe, 40·2%).

Hydrolysis of the Methylated Gum and Identification of the Neutral Sugars.—The methylated gum (8·0 g.) was dissolved in 2N-sulphuric acid (125 c.c.) and kept at room temperature for 10 days. The solution was then heated at 100° for 20 hr., cooled, and carefully neutralised with barium hydroxide. After carbon dioxide had been bubbled through the mixture to remove excess of hydroxide as barium carbonate, the precipitated barium salts were removed and the solution was taken to dryness. The resulting mixture of sugars was separated on cellulose, with light petroleum (b. p. 100—120°)–butan-1-ol (6 : 4), saturated with water, as eluant, to give four fractions containing neutral sugars, and elution with water gave a mixture of acidic substances (as barium salts) (E) which was examined later.

Fraction A. The syrup (0·90 g.) had $[\alpha]_D^{18}$ +111° (*c*, 0·96 in H_2O) and R_G 0·88 in solvent *B* (Found: OMe, 52·0. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%), and was identified as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose by conversion into the aniline derivative, m. p. and mixed m. p. 190°, $[\alpha]_D^{16}$ −63°→+34° (equil.) (*c*, 0·83 in Me_2CO).

Fraction B. The syrup (0·84 g.) had $[\alpha]_D^{15}$ +86° (*c*, 1·07 in H_2O) and R_G 0·71 (Found: OMe, 42·4. Calc. for $C_9H_{18}O_6$: OMe, 41·9%), and was identified as 2 : 3 : 6-tri-*O*-methyl-D-galactose by conversion into 2 : 3 : 6-tri-*O*-methyl-D-galactono-1 : 4-lactone, m. p. and mixed m. p. 98°, $[\alpha]_D^{17}$ −40°→−29° (equil.) (*c*, 0·55 in H_2O). As the 2 : 3 : 6- and the 2 : 4 : 6-trimethyl ether of D-galactose travel at similar rates on the chromatogram evidence for the presence of the 2 : 4 : 6-isomer in this fraction was sought but none was found: all attempts to prepare the aniline derivative failed and chromatographic examination of the tri-*O*-methylgalactonolactone indicated the presence of only the one component.

Fraction C. The sugar (0·28 g.) had $[\alpha]_D^{16}$ +37° (equil.) (*c*, 0·95 in H_2O), $[\alpha]_D^{15}$ +11° (equil.)

(*c*, 1·93 in EtOH), and R_G 0·55 (Found : OMe, 18·5. Calc. for $C_7H_{14}O_5$: OMe, 17·4%), and crystallised [9] on removal of solvent, m. p. 115°. The methyl glycoside of the sugar was unattacked by periodate and the derived 3-*O*-methyl-L-rhamnono-1 : 4-lactone had $[\alpha]_D^{16}$ −20° → −18° (equil.) (*c*, 1·6 in H_2O).

Fraction D. The syrup (23 mg.) contained two sugars with R_G 0·55 and 0·45 and was examined after combination with a later fraction.

Examination of the Acidic Fraction.—The mixture of barium salts (E) was converted into the corresponding mixture of acids by removal of barium ions with Amberlite resin IR-120(H). The mixture was separated into two fractions by partition on cellulose, with, as eluant, butan-1-ol 50% saturated with water to which glacial acetic acid (5%, v/v) was added. Fraction 1 (0·70 g.) contained a main component having R_G 0·81 in solvent *C* together with a trace of a substance with R_G 0·95, and was unchanged by hot 2N-sulphuric acid. Fraction 2 (3·1 g.) contained substances with R_G less than 0·81 and was further hydrolysed by 2N-sulphuric acid at 100° for 24 hr. and the hydrolysate was neutralised with barium carbonate. The neutral sugars were separated from the barium salts of the acidic components by partition on cellulose, with light petroleum (b. p. 100—120°)–butan-1-ol, saturated with water, butan-1-ol saturated with water, and water as eluants. Fraction B(i) (45 mg.) had R_G 0·71 (solvent *B*) and fraction C(i) (110 mg.) had R_G 0·55. Fraction D(i) (33 mg.) contained sugars of R_G 0·55 and 0·45 and was combined with fraction D (total 56 mg.), $[\alpha]_D^{16}$ +57° (*c*, 0·63 in H_2O) [Found : OMe, 25·2. A mixture of di-*O*-methyl-hexose and mono-*O*-methylrhamnose (2 : 1) requires OMe, 25·7%]. Fraction F (20 mg.) travelled on the chromatogram at the same rate as rhamnose (R_G 0·30) and fraction G (20 mg.) had R_G 0·25 but was not examined further. Fraction 3, obtained as barium salts by elution of the column with water, was converted into a mixture of acids by de-ionisation with Amberlite resin IR-120(H), and when taken to dryness gave a syrup (1·2 g.) in which one main component (R_G 0·45 in solvent *C*) was present, together with traces of other compounds.

Reduction of the Acidic Fractions with Lithium Aluminium Hydride.—The two acidic fractions 1 and 2 were combined (2·1 g.) and refluxed with methanolic 2% hydrogen chloride for 10 hr. After neutralisation with silver carbonate, the solution was taken to dryness, the resulting syrup was dissolved in dry tetrahydrofuran (10 c.c.), and the solution was added slowly to lithium aluminium hydride (1·0 g.) in tetrahydrofuran (10 c.c.). After 4 hr., the excess of hydride was destroyed by water, the solution was acidified with dilute sulphuric acid, the sulphate and aluminium ions were removed as precipitates on addition of barium hydroxide, and the barium and lithium ions were removed as the insoluble carbonates. The resulting solution was taken to dryness, to yield a syrup (1·1 g.), which was hydrolysed by N-sulphuric acid at 100° for 16 hr., and the hydrolysate was separated on cellulose, eluants being light petroleum (b. p. 100—120°)–butan-1-ol, saturated with water, and butan-1-ol 50% saturated with water, to give four fractions.

Fraction a. The syrup (0·111 g.) had $[\alpha]_D^{16}$ +73° (*c*, 0·63 in H_2O) and R_G 0·85 in solvent *B* (Found : OMe, 40·3. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). Methylation of the sugar and hydrolysis of the resulting methyl glycoside yielded 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose, m. p. 82° and $[\alpha]_D^{14}$ +81° (equil.) (*c*, 0·32 in H_2O), and the sugar was identified as 2 : 3 : 4-tri-*O*-methyl-D-glucose by conversion into the aniline derivative, m. p. 146°.

Fraction b. The sugar (0·068 g.), $[\alpha]_D^{16}$ +85° (*c*, 0·99 in H_2O) and R_G 0·71 (Found : OMe, 40·5. Calc. for $C_9H_{18}O_6$: OMe, 41·9%), was identified as 2 : 3 : 6-tri-*O*-methyl-D-galactose by conversion into 2 : 3 : 6-tri-*O*-methyl-D-galactono-1 : 4-lactone, m. p. and mixed m. p. 97°.

Fraction c. The sugar (0·154 g.), $[\alpha]_D^{16}$ +14° (*c*, 0·57 in EtOH) and R_G 0·55, crystallised and had m. p. and mixed m. p. (with 3-*O*-methyl-L-rhamnose) 115° (Found : OMe, 17·0. Calc. for $C_7H_{14}O_5$: OMe, 17·4%).

Fraction d. The syrup (0·25 g.) had $[\alpha]_D^{16}$ +103° (*c*, 0·84 in H_2O) and R_G 0·46 in solvent *B*, and was identified as 2 : 3-di-*O*-methyl-D-galactose by conversion into the aniline derivative, m. p. and mixed m. p. 154°, $[\alpha]_D^{19}$ −46·5° → +12° (equil.) (*c*, 1·0 in EtOH).[17]

Reduction of the Methylated Gum.—The methylated gum (0·50 g.) was dissolved in dry tetrahydrofuran (10 c.c.) and added slowly to lithium aluminium hydride (0·25 g.) in tetrahydrofuran (10 c.c.). After 2 hr. at room temperature, the solution was refluxed for 2 hr. and set aside overnight. Excess of hydride was destroyed by ethyl acetate, and the solution was acidified with dilute sulphuric acid and extracted with chloroform. The chloroform extract yielded the reduced methylated gum (A) (0·39 g.), $[\alpha]_D^{16}$ +46° (*c*, 1·44 in $CHCl_3$) (Found : OMe, 31·6%).

The reduced methylated gum A (0·30 g.) was further methylated by four treatments with

[17] Bell and Greville, *J.*, 1955, 1136.

methyl iodide and silver oxide, to give reduced methylated gum (B) (0·26 g.), $[\alpha]_D^{17}$ +34° (*c*, 1·12 in $CHCl_3$) (Found : OMe, 40·8%).

Hydrolysis of the Reduced Methylated Gums.—The reduced methylated gums (*ca.* 100 mg.) were hydrolysed by formic acid at 100° for 4 hr. and after removal of formic acid with N-hydrochloric acid at 100° for 16 hr. After neutralisation with silver carbonate the hydrolysates were separated on extractive-free Whatman 3MM paper with solvent *B*. The appropriate sections of the papers were extracted with hot methanol, and the extracts were filtered and taken to dryness. The annexed weights of sugars are corrected for blanks.

Sugar	R_G in solvent *B*	Wt. of sugar from gum A (89·1 mg.)	Wt. of sugar from gum B (86·9 mg.)
Tetra-*O*-methylglucose	1·00	—	5·1
Tetra-*O*-methylgalactose	0·88	15·9	12·7
Tri-*O*-methylglucose	0·85	15·9	—
Tri-*O*-methylgalactose	0·71	16·4	28·4
Mono-*O*-methylrhamnose	0·55	17·2	15·4
Di-*O*-methylgalactose	0·46	20·8	3·6
Rhamnose	0·30	1·2	0·8

Purification and Properties of Khaya senegalensis *Gum.*—The gum was obtained as colourless to dark brown nodules admixed with small particles of bark. One particular nodule had OMe, 2·2, and OAc, 2·7%, and chromatographic examination of the hydrolysate showed galactose, arabinose, rhamnose, and a complex mixture of acidic substances. The gum was purified by dissolving it in 4% sodium hydroxide solution, removing the mechanical impurities at the centrifuge, acidifying the resulting solution with hydrochloric acid, and precipitating the polysaccharide with ethanol. After three reprecipitations from aqueous solution with ethanol, the gum was isolated as a white powder, $[\alpha]_D^{16}$ +124° (*c*, 0·97 in H_2O) [Found : equiv., 412 (by titration); sulphated ash, 2·2; OMe, 1·2%].

Partial Hydrolysis of K. senegalensis *Gum.*—The purified gum (2·30 g.) was heated with N-sulphuric acid at 100° for 6 hr., the hydrolysate was neutralised with barium hydroxide, the excess of alkali was rapidly destroyed with carbon dioxide, and the filtrate was taken to dryness. The residue was fractionated on cellulose, eluant being butan-1-ol saturated with water plus 5% ethanol, to give four fractions. Fraction 1 (0·091 g.) had $[\alpha]_D^{18}$ +10° (equil.) (*c*, 1·02 in H_2O) and after recrystallisation from moist butan-1-ol had m. p. and mixed m. p. (with L-rhamnose hydrate) 92°. Fraction 2 (0·048 g.) had $[\alpha]_D^{17}$ +113° (equil.) (*c*, 0·79 in H_2O) and after recrystallisation from ethanol had m. p. and mixed m. p. (with L-arabinose) 156°. Fraction 3 (0·370 g.) had $[\alpha]_D^{18}$ +80° (equil.) (*c*, 2·14 in H_2O) and after recrystallisation from methanol had m. p. and mixed m. p. (with D-galactose) 164°. Fraction 4 was obtained by elution of the cellulose with water and consisted of the barium salts of acidic substances. The barium ions were removed with Amberlite resin IR-120, and the acidic fraction was freeze-dried to give a yellow powder (0·87 g.). Chromatographic examination in solvent *D* indicated a complex mixture of acids, R_{Gal} 0·80 (intense), 0·40, 0·19, and 0·09, similar to those formed on partial hydrolysis of *K. grandifolia* gum. The fraction had equiv. 348 (by titration) and hydrolysis with 2N-sulphuric acid gave rhamnose and galactose. A portion of the fraction was converted into the methyl ester methyl glycoside by heating it with methanolic hydrogen chloride, then reduced with potassium borohydride, and the product was hydrolysed and shown by chromatography to contain rhamnose, 4-*O*-methylglucose, galactose, and a trace of glucose.

The authors thank Dr. R. J. McIlroy for providing the samples of the gums, and Drs. D. J. Bell and G. D. Greville for samples of 2 : 3-di-*O*-methyl-D-galactose and its aniline derivative. Thanks are also expressed to the Rockefeller Foundation, Imperial Chemical Industries Limited, and the Distillers Company Ltd. for grants.

CHEMISTRY DEPARTMENT, UNIVERSITY OF EDINBURGH. [*Received, October 6th*, 1955.]

207. *Conductimetric Studies in Ketonic Solvents. Part II.* Water in Ketones.*

By S. R. C. Hughes.

The density and viscosity data for acetone containing water can be correlated with the water content by linear equations; similar correlations have been made for ethyl methyl ketone containing water. The conductivity data for potassium iodide in acetone and in ethyl methyl ketone, related to water content, show contrasting rôles of water in these two media.

Correlation of Physical Data.—In Part I * it was inferred that conductivity measurements hitherto made in acetone are modified by the presence of considerable proportions of water. These studies are now extended so as to permit comparison between this solvent and ethyl methyl ketone.

The available density and viscosity data at 25° for acetone containing up to 5% of water can be summarized by the linear equations (1) and (2) (where x is the weight % of water), as shown by the correlations in Table 1.

$$d_4^{25} = 0{\cdot}78345 + 0{\cdot}003067x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$\eta_{10}^{25} = 0{\cdot}003000 + 0{\cdot}0001667x \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

TABLE 1. *Physical data for acetone–water mixtures at 25°.*

Source	x (H_2O, %)	d_4^{25}	Deviation from Eqn. (1)	$10^4\eta_{10}^{25}$	Deviation from Eqn. (2)
Part I	0·18	$0{\cdot}7840_0$	$0{\cdot}0000_0$	—	—
,,	0·22	$0{\cdot}7841_3$	$0{\cdot}0000_1$	—	—
Ref. 1	$(0{\cdot}34_3)$	0·7845	—	30·40	−0·000017
Ref. 2	0·45	0·7849	$0{\cdot}0000_7$	32·00	$0{\cdot}00012_5$
Ref. 3	$(0{\cdot}46_6)$	$0{\cdot}7848_8$	—	30·93	$0{\cdot}00001_8$
Ref. 4	$(0{\cdot}51_5)$	$0{\cdot}7850_3$	—	$30{\cdot}7_5$	$-0{\cdot}00001_1$
Ref. 4	$0{\cdot}76_5$ *	$0{\cdot}7858_7$	$0{\cdot}0000_7$	$30{\cdot}9_5$	$-0{\cdot}00003_2$
Part I	0·87	$0{\cdot}7861_2$	$0{\cdot}0000_1$	—	—
Ref. 5	$(0{\cdot}89_7)$	0·7862	—	$31{\cdot}5_8$	$0{\cdot}00000_8$
Ref. 4	$1{\cdot}00_8$ *	$0{\cdot}7865_1$	$-0{\cdot}0000_1$	$31{\cdot}2_0$	$-0{\cdot}00004_6$
,,	$1{\cdot}51_1$ *	$0{\cdot}7880_3$	$-0{\cdot}0000_7$	—	—
Part I	1·65	$0{\cdot}7882_3$	$-0{\cdot}0002_9$	—	
Ref. 2	2·89	0·7922	$-0{\cdot}0001_3$	34·9	$0{\cdot}00000_8$
,,	5·35	0·7997	$0{\cdot}0001_4$	37·8	$0{\cdot}00011_3$

* Water contents in parentheses are calculated from the authors' densities by Eqn. (1). Those marked with asterisks refer to wetted acetones in which such initial water contents are included. All other water contents are based upon analyses by Karl Fischer's method.

Density and viscosity data determined here for wetted ethyl methyl ketone containing up to 4·728% of water may similarly be summarized by equations (3) and (4), whose correlation is illustrated in Table 2.

$$d_4^{25} = 0{\cdot}79978 + 0{\cdot}002645_8x \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$\eta_{10}^{25} = 0{\cdot}003792 + 0{\cdot}0001275x \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The relative dielectric constants of ethyl methyl ketone–water mixtures at 25° are found to be adequately reproduced up to 5% of water by equation (5):

$$D = 18{\cdot}4 + 0{\cdot}701x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Conductivity of Potassium Iodide in Wetted Acetone and in Wetted Ethyl Methyl Ketone.—In Part I are given the Λ_0 and K values for potassium iodide in acetone samples of reported

* Part I, *J.*, 1954, 953.

[1] Reynolds and Kraus, *J. Amer. Chem. Soc.*, 1948, **70**, 1709.
[2] Olsen and Konecny, *ibid.*, 1953, **75**, 5801.
[3] International Conference (Brussels), *J. Chim. phys.*, 1928, **25**, 401.
[4] Data of Ross-Kane: Hartley and O. L. Hughes, *Phil. Mag.*, 1933, **54**, 975.
[5] Walden, Ulich, and Busch, *Z. phys. Chem.*, 1926, **123**, 429.

density, whose water contents can therefore be estimated by application of Equation (1). Data relating to potassium iodide in ethyl methyl ketone and mixtures of this solvent with water are reported in Tables 3 and 4, in which κ is the conductance of the solvent in mhos and c the concentration of potassium iodide in moles/l. It is thus possible to calculate Bjerrum parameters and Walden products for potassium iodide in these media, the data being summarized in Figs. 1 and 2.

TABLE 2. *Physical data for ethyl methyl ketone–water mixtures at 25°.*

x (H_2O, %)	d_4^{25}	Deviation from Eqn. (3)	$10^4\eta_0^{25}$	Deviation from Eqn. (4)	x (H_2O, %)	d_4^{25}	Deviation from Eqn. (3)	$10^4\eta_0^{25}$	Deviation from Eqn. (4)
0 *	0·7995$_6$	−0·0002$_0$	37·9$_9$	0·00000$_7$	1·176	—	—	39·4$_0$	−0·00000$_9$
0 †	0·7997$_6$	−0·0000$_2$	38·1$_5$	0·00002$_3$	1·184	—	—	39·3$_7$	−0·00000$_7$
0·2031	0·8003$_3$	0·0000$_1$	38·3$_9$	0·00001$_2$	1·338	0·8032$_0$	−0·0001$_2$	39·2$_4$	−0·00003$_7$
0·2474	0·8004$_1$	−0·0000$_2$	—	—	1·700	0·8041$_5$	−0·0001$_9$	40·0$_2$	−0·00000$_4$
0·3329	0·8006$_8$	0·0000$_2$	—	—	2·191	—	—	40·6$_5$	−0·00000$_6$
0·4520	0·8009$_4$	−0·0000$_2$	38·4$_5$	−0·00000$_5$	2·628	0·8065$_0$	−0·0002$_2$	41·1$_3$	−0·00001$_3$
0·4780	—	—	38·5$_6$	−0·00000$_3$	3·588	0·8095$_0$	0·0002$_3$	—	—
0·5100	0·8011$_3$	0·0000$_0$	—	—	4·713	—	—	44·0$_0$	−0·00000$_7$
0·5350	0·8012$_1$	0·0000$_1$	38·4$_9$	−0·00001$_1$	4·728	0·8125$_1$	0·0002$_3$	43·8$_0$	0·00001$_4$
0·7333	—	—	38·8$_0$	−0·00000$_5$					
0·8321	0·8017$_3$	0·0002$_5$	38·8$_0$	−0·00001$_8$					
0·8676	0·8020$_9$	0·0000$_1$	39·1$_4$	0·00001$_1$					
0·9060	—	—	39·1$_3$	0·00000$_4$					
0·9519	0·80209	−0·0002$_1$	—	—					

* Ethyl methyl ketone protected from laboratory atmosphere in the dry space. In the viscosity determinations, silica-gel guard tubes were fitted to the viscometer.

† Solvent handled in laboratory atmosphere. Guard tubes omitted from viscometer.

TABLE 3. *Conductivity of potassium iodide in dry ethyl methyl ketone at 25°.*

$D = 18{\cdot}4$.[7] By Fuoss plot: $\Lambda_0 = 150{\cdot}8$, $K = 2{\cdot}125 \times 10^{-3}$.

$10^3\kappa$	10^4c	Λ	$10^3\kappa$	10^4c	Λ	$10^3\kappa$	10^4c	Λ	$10^3\kappa$	10^4c	Λ
3·380	0·7132	142·0	3·841	2·803	129·5	2·808	4·777	122·6	3·841	6·455	117·8
2·808	0·8616	141·1	4·609	3·125	128·3	3·380	4·932	122·3	3·380	6·776	117·1
4·609	1·485	136·9	2·808	3·388	127·5	3·841	5·112	121·4	2·808	7·313	115·5
3·380	1·545	136·6	3·380	3·534	126·9	4·609	5·271	119·9	4·609	7·456	115·0
2·808	2·040	133·8	4·609	4·176	123·8	2·808	6·232	118·6	3·380	8·009	114·2
3·380	2·389	131·7									

TABLE 4. *Conductivity of potassium iodide in wetted ethyl methyl ketone at 25°.**

10^4c	Λ	10^4c	Λ	10^4c	Λ	10^4c	Λ	10^4c	Λ
$x = 0{\cdot}301\%$; $10^7\kappa = 0{\cdot}389$		$x = 0{\cdot}510\%$; $10^7\kappa = 0{\cdot}830$		$x = 0{\cdot}537\%$; $10^7\kappa = 0{\cdot}510$		$x = 0{\cdot}906\%$; $10^7\kappa = 0{\cdot}492$		$x = 0{\cdot}952\%$; $10^7\kappa = 1{\cdot}44$	
0·5614	142·1	0·2580	140·9	0·9928	138·5	0·8930	136·6	0·5830	139·1
1·213	137·4	0·7003	139·4	1·923	133·2	2·024	130·4	2·046	131·2
1·961	133·4	1·610	134·7	3·248	127·6	3·395	125·4	3·518	125·1
2·707	130·0	2·354	130·8	4·379	123·7	4·900	120·6	5·001	120·0
3·580	126·0	3·830	125·4	$\Lambda_0 = 148{\cdot}4$;		7·160	115·1	6·627	116·1
$\Lambda_0 = 148{\cdot}8$; $10^3K = 2{\cdot}57$		$\Lambda_0 = 148{\cdot}2$; $10^3K = 2{\cdot}55_4$		$10^3K = 2{\cdot}50_5$		$\Lambda_0 = 145{\cdot}2$; $10^3K = 2{\cdot}76_4$		$\Lambda_0 = 145{\cdot}6$; $10^3K = 2{\cdot}58_4$	
$x = 1{\cdot}338\%$; $10^7\kappa = 3{\cdot}63$		$x = 1{\cdot}700\%$; $10^7\kappa = 3{\cdot}20$		$x = 2{\cdot}628\%$; $10^7\kappa = 11{\cdot}27$		$x = 3{\cdot}588\%$; $10^7\kappa = 6{\cdot}10$		$x = 4{\cdot}728\%$; $10^7\kappa = 8{\cdot}11$	
1·042	133·3	0·9315	131·3	1·331	120·8	0·8441	121·4	0·6415	115·3
2·052	127·9	2·080	127·3	3·046	117·6	1·834	117·3	1·538	112·7
2·900	125·3	3·103	122·1	5·564	111·6	3·101	114·2	2·470	110·1
4·028	121·4	4·016	120·0	$\Lambda_0 = 132{\cdot}1$;		4·636	110·0	4·051	106·5
5·637	117·2	$\Lambda_0 = 139{\cdot}0$;		$10^3K = 4{\cdot}06$		5·762	108·6	$\Lambda_0 = 120{\cdot}6$;	
$\Lambda_0 = 142{\cdot}5$; $10^3K = 2{\cdot}99_5$		$10^3K = 3{\cdot}45$				$\Lambda_0 = 127{\cdot}4$; $10^3K = 4{\cdot}87_2$		$10^3K = 5{\cdot}08$	

* Values of Λ_0 and K at the bottom of each section are obtained from the Fuoss plot.

EXPERIMENTAL

Conductivity Measurements and Purification of Solvents.—These followed the procedures previously described for Grade I acetone (Part I). Additions of conductivity water to dry ethyl

methyl ketone were made from a weight burette. Densities were determined in a 100-c.c. graduated pyknometer designed for handling within the dry-space (*loc. cit.*). For viscosity measurement a Technico No. 0 viscometer was used; it was calibrated with water which gave a flow time of 22 min. 35·0 sec. at 25°. Except where otherwise stated (see footnotes to Table 2), the dry solvent and samples containing less than 1% of water were protected from the laboratory atmosphere by dry-space technique.

Dielectric Constants.—Comparative values for these for wetted samples of ethyl methyl ketone were measured on a heterodyne-beat bridge. The solvent was contained in a double-surface, silvered, condenser cell calibrated with dry ethyl methyl ketone for which the value $D_{25} = 18{\cdot}4$ was adopted.[7] Capacitances were measured by parallel replacement with a Muirhead precision air-condenser.

Discussion

The contrasting physical interactions of acetone and of ethyl methyl ketone with water make it more practicable to obtain the latter ketone dry. The author believes that the alumina and dry-space techniques (described in Part I) have achieved this object; the

Fig. 1. Fig. 2.

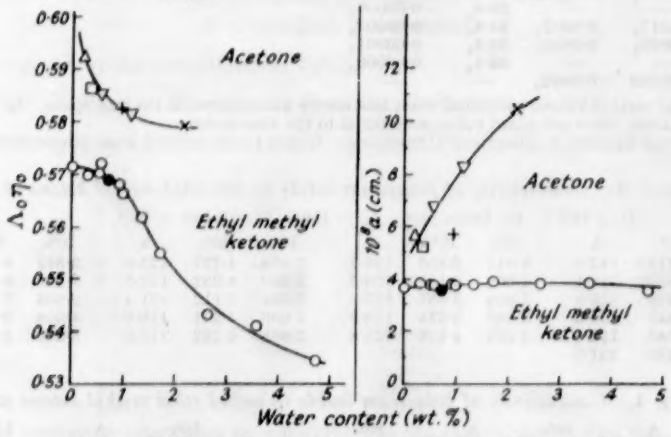


Fig. 1. *Walden product for potassium iodide in wet ketones at 25°.*
Fig. 2. *Bjerrum product for potassium iodide in wet ketones at 25°.*

○ Present work.
△ Part I.
□ Reynolds and Kraus.[1]
▽ Ross-Kane.[4]
\+ Walden, Ulich, and Busch.[5]
× Bauer.[6]
● Walden and Birr.[8]

physical data at the head of Table 2 and the conductivity of potassium iodide in the unwetted solvent confirm this view. The density reported by Walden and Birr [8] for their ethyl methyl ketone shows it to have contained 0·69$_2$% of water by Equation (3); the resultant viscosity from Equation (4) is in fair agreement with their value. The conductivity data for potassium iodide recorded by Walden and Birr, recalculated by Fuoss's method, show good correlation with values measured here in wetted ethyl methyl ketone (Figs. 1 and 2).

The Walden product ($\Lambda_{0{\cdot}7\%}^{25}$) for potassium iodide in acetone descends sharply with initial increase of solvent water content (Fig. 1). The behaviour reported for lithium bromide in these media is similar.[3] Such variations in acetone have been largely ascribed to increase in hydrodynamic cation radius.[4] The Bjerrum distance for potassium iodide

[6] Bauer, *Ann. Physik*, 1930, **6**, 253.
[7] Sacks and Fuoss, *J. Amer. Chem. Soc.*, 1953, **75**, 5712.
[8] Walden and Birr, *Z. phys. Chem.*, 1931, *A*, **153**, 1.

in acetone also rises markedly with increase in water content of the solvent (Fig. 2). The Stokes and the Bjerrum parameters correspond, in this instance, closely enough for their mutual solution to be effected and their variations are consistent with a rapid increase in cation radius with increase in water content of the solvent (Part I).

In dry ethyl methyl ketone, the product $\Lambda_0\eta_0^{25}$ for potassium iodide is less than that found in the wettest acetone solution on record and remains practically constant over the first 1% of added water; from 1% to 3% it descends steeply, but less so for additions of water above 3%. The Bjerrum parameters for potassium iodide, both in dry ethyl methyl ketone and in solvent containing up to 4·7% of water, remain within 0·2 Å of the crystallographic distance for this salt. It is evident that there is no correspondence between Stokes and Bjerrum radii in these media, the former being considerably larger and showing some variation with water content of the solvent.

Disparity between Stokes and Bjerrum radii may be due to mathematical deficiencies, superimposed in some cases upon actual de-solvation caused by electrostatic association.[7,9–11] Agreement between the iodide radii, extracted in Part I, and the crystallographic value suggests that where these parameters are compatible the mathematical deficiencies may be small. If we assume, therefore, that some physical reality attaches to the two parameters in the cases analyzed here, the contrast between the two ketonic solvents becomes clearer.

The cationic solvation sheath for potassium iodide in moist acetone is a sufficiently stable structure to withstand ion association, and it increases with added water, the increase being the greater at lower water contents. That in dry, and in 1% wetted, ethyl methyl ketone, while greater than the acetone sheath radius by some 1 Å (with assumption of an unsolvated iodide ion, $r_{I^-} = 2{\cdot}16$ Å) is unable to withstand ion association. When ethyl methyl ketone is wetted up to 4·7% the hydrodynamic cation radius parameter attains approximately the value found in acetone containing $0{\cdot}51_5$% of water.

These comparisons indicate that the water contained in acetone is highly effective in solvating cations, whereas that in wetted ethyl methyl ketone is less so. Furthermore, the water in acetone solvates the potassium ion with a peculiar stability dependent, perhaps, on ionic co-ordination number. The re-analyzed conductivity data of Walden, Ulich, and Busch [5] and of Dippy, Jenkins, and Page [12] for sodium iodide in acetone show this salt to have a greater Stokes cation radius than potassium iodide but a smaller Bjerrum parameter, greater, however, than its crystallographic distance. Olsen and Konecny's observations [2] show a sharp increase in hydrodynamic radius on wetting lithium bromide in acetone, whereas the Bjerrum parameters remain close to the crystallographic distance up to 5% of total water content. It will be shown in a subsequent communication that relative alkali-cation association parameters, in dry ketonic solvents, stand in the reverse order to those in acetone.

Fuoss and his co-workers [7,9–11] find methanol to be a more effective solvating agent when depolymerized [13] by suitable diluents than when in its normal associated state. An analogous explanation of the contrasts seen here, between the behaviour of water in acetone and that in ethyl methyl ketone, seems reasonable. The high cation-solvating efficiency of water in acetone could be ascribed to the depolymerization of water by this solvent; the different rôle played by water in ethyl methyl ketone is consistent with its remaining associated in this medium. The contrasting physical interactions of these two ketones with water (*e.g.*, miscibility, vapour pressure) do not contradict this hypothesis.

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CHELSEA POLYTECHNIC, LONDON, S.W.3. [*Received, October 17th*, 1955.]

[9] Miller and Fuoss, *J. Amer. Chem. Soc.*, 1953, **75**, 3076.
[10] Sadek and Fuoss, *ibid.*, 1954, **76**, 5897.
[11] *Idem, ibid.*, p. 5905.
[12] Dippy, Jenkins, and Page, *J.*, 1939, 1386.
[13] Mecke, *Discuss. Faraday Soc.*, 1950, **9**, 161.

208. *The Thermal Decomposition of Octadeuterocyclobutane and Octafluorocyclobutane.*

By B. F. Gray and H. O. Pritchard.

The high-pressure rate constant for the decomposition of [$^2H_8$]*cyclo*butane at 443° is greater than that for ordinary *cyclo*butane and the fall-off of the rate constant takes place at a slightly higher pressure for the deuterated species. The decomposition of octafluoro*cyclo*butane is shown to be a complex process unsuitable for testing theories of unimolecular reactions.

Slater [1] has pointed out that his theory of unimolecular reactions leads to the expectation that an isotope effect should be observable in the thermal decompositions of *cyclo*propane and *cyclo*butane. We have studied the pressure dependence of the rate constant for the thermal decomposition of [$^2H_8$]*cyclo*butane, and in an attempt to gain more information about the nature of the isotope effect, we have also studied the decomposition of octafluoro-*cyclo*butane on the (mistaken) supposition that the substitution of fluorine for hydrogen might only be accompanied by a large pseudo-isotope effect.

Experimental

Thermal Decomposition of Octadeuterocyclobutane.—A sample of [$^2H_8$]*cyclo*butane of 99·7% isotopic purity was kindly given to us by Dr. D. G. Rea; after bulb-to-bulb distillation, mass-spectrometric analysis confirmed the deuterium content of the material, and showed that no impurities were present. The details of apparatus and procedure are identical with those already described for the parallel study on normal *cyclo*butane [2] except that, owing to the rather greater rate constant in the present experiments and the limited amount of substance available, the temperature of the reaction vessel used was 442·6° instead of about 448°. Ten runs taken to about 30% decomposition were performed, covering the pressure range 1·25—0·005 cm., and extrapolation of k against $1/p$ led to the value $k_\infty(C_4D_8) = 5{\cdot}5 \times 10^{-4}$ sec.$^{-1}$ at 442·6° as compared with $k_\infty(C_4H_8) = 2{\cdot}6 \times 10^{-4}$ sec.$^{-1}$ calculated for the same temperature. The individual results are plotted in the Figure showing the variation of log k/k_∞ with log p for [$^2H_8$]*cyclo*butane together with that for ordinary *cyclo*butane; the fall-off is shifted very slightly to higher pressures upon deuteration of the molecule.

Thermal Decomposition of Octafluorocyclobutane.—Octafluoro*cyclo*butane was prepared by heating tetrafluoroethylene in a Pyrex vessel for about 30 hr. at 330°; at this temperature, the equilibrium $2C_2F_4 \rightleftharpoons C_4F_8$ lies well to the right.[3] The dimer was purified by low-temperature fractional distillation. Experiments were carried out in a 1-l. spherical Pyrex reaction vessel kept by thermostat at 530°, the course of the reaction being studied by pressure measurement and by analysis of the products. The behaviour of the system varied markedly according to conditions, *e.g.*, pressure, presence of impurities and ageing of the reaction vessel, and the most important effects are dealt with in the following five sections:

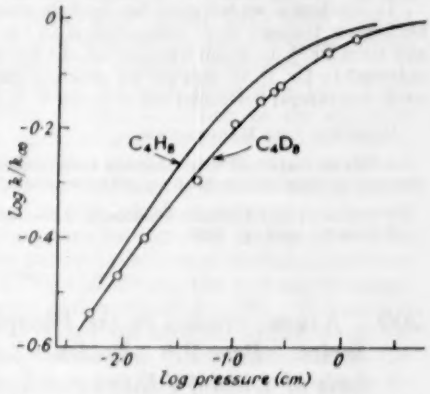
(i) In an unaged vessel a very rapid reaction took place in which the pressure of the system doubled in about 1—1½ min. and then remained approximately constant; the vessel could be aged by leaving tetrafluoroethylene in it overnight, but the effect was immediately reversed upon the admission of air. If during the progress of rapid decomposition the mixture was frozen out with liquid nitrogen and then allowed to evaporate, a 30% decrease in pressure was observed and a thin layer of polymer was formed in the cold part of the system; this is consistent either with the presence of long-lived free radicals in the mixture, or with the presence of hydrogen fluoride or oxygen (originating from the walls) which are known to polymerize tetrafluoroethylene under suitable conditions.

(ii) Atkinson and Trenwith reported a first-order rate constant for the decomposition of octafluoro*cyclo*butane of about 6×10^{-5} sec.$^{-1}$ at 530° in the pressure range 35—45 cm. Our experiments at this temperature and at 30 cm. initial pressure (p_0) were in excellent agreement with these results: equilibrium was reached in about 10 min., and mass-spectral analysis of the equilibrium mixture confirmed that, apart from traces of carbon monoxide and silicon tetrafluoride, only octafluoro*cyclo*butane and tetrafluoroethylene were present; on the basis of

[1] Slater, *Phil. Trans.*, 1953, *A*, **246**, 57.
[2] Pritchard, Sowden, and Trotman-Dickenson, *Proc. Roy. Soc.*, 1953, *A*, **218**, 416.
[3] Atkinson and Trenwith, *J.*, 1953, 2082.

Atkinson and Trenwith's interpretation of a first-order decomposition opposed by a second-order dimerization, we obtained the first-order rate constant of 3×10^{-4} sec.$^{-1}$. If, however, the equilibrium mixture remained in the vessel, there was a very gradual increase in pressure, having a zero-order rate constant of 0·01 cm. min.$^{-1}$ to a final pressure of $9{\cdot}6p_0$. The final equilibrium mixture was shown by mass-spectrometric analysis to consist mainly of silicon tetrafluoride and carbon monoxide, some water (which can only arise from hydroxyl ions in the glass), and a trace of tetrafluoroethylene; volatile boron compounds were also shown to be present in the mixture by rapidly pumping out the contents of the vessel into a trap containing water and applying the standard qualitative tests for boron.

(iii) A series of runs were made covering the pressure range 30—0·03 cm., but no decrease in the rate constant was detected—in fact, it apparently increased. At the lower pressures the condition of equilibrium became less apparent and often there was only an inflection in the



The dependence of the rate of decomposition of cyclo*butane and* [$^2H_8$]cyclo*butane on pressure.*

p–t curve before the steady rise to $9{\cdot}6p_0$ became dominant; in those cases where the first equilibrium could be detected with reasonable certainty, the following apparent first-order constants were obtained:

p_0 (cm.)	31·55	5·0	1·0	0·16	0·08	0·03
k (sec.$^{-1}$) $\times 10^5$	3	10	15	120	237	330

It is clear that the decomposition of octafluoro*cyclo*butane is not a simple unimolecular process, and the following additional experiments were therefore performed.

(iv) In a run with 1 cm. of octafluoro*cyclo*butane and 1·8 cm. of water, the approach to the first equilibrium was unaffected, but the rate of the zero-order pressure rise was *decreased* by a factor of 10 and the final pressure (after allowance for the added water) was only $8{\cdot}9p_0$ instead of $9{\cdot}6p_0$, demonstrating that water, both in the solid and in the vapour phase, is fundamentally involved in the zero-order process.

(v) Several runs were carried out in the presence of about 10% of toluene: the general behaviour of the p–t curve remained unchanged except that during the first 10 min. the pressure varied in a periodic manner; the number and positions of the pressure maxima and minima were quite reproducible from one run to another. Mass-spectrometric analysis of the mixture showed it to contain a very large number of partially fluorinated hydrocarbons, up to and including a mass number of 225, strongly indicative of a complex free-radical process.

Discussion.—It is not an easy matter to correlate the results for octadeutero*cyclo*butane with Slater's theory, which is dependent on a complete vibrational analysis of both molecules and the suitable choice of a critical co-ordinate. One can say, however, that if the critical energy of activation for both molecules is the same,* the critical co-ordinate is neither a C–H nor an H–H distance, because the theory would then predict $k_\infty(C_4H_8)/k_\infty(C_4D_8) \approx \sqrt{2}$ in both cases, as opposed to the ratio of $\frac{1}{2}$ actually found; our observations are, however, consistent with Slater's theory in that the ***higher*** value

* We are unable now to undertake experiments which would be sufficiently accurate to detect a small difference in the activation energies for the decomposition of these molecules.

of k_∞ is associated with the fall-off taking place at a *higher* pressure than for the normal molecule.

The octafluoro*cyclo*butane experiments show that, even allowing for the complication of handling fluorocarbons in a glass system, the thermal decomposition of octafluoro*cyclo*butane is not a simple unimolecular reaction and thus not suitable for energy-transfer studies. We are not prepared to speculate upon the nature of the reactions taking place, but it seems likely that the initial decomposition proceeds by fission of a C–C bond; the best estimate for the C–C dissociation energy in *cyclo*butane is 74 kcal./mole,[4,*] and whilst *cyclo*butane itself decomposes by a non-radical mechanism having an activation energy of 62·8 kcal./mole, the decomposition of octafluoro*cyclo*butane has an activation energy of 74·1 kcal./mole and is attended by obvious free-radical effects.

In conclusion we acknowledge the help received from Drs. R. G. Sowden and A. F. Trotman-Dickenson through their collaboration in the early stages of the octafluoro*cyclo*butane work, and from Dr. J. C. Robb who carried out the mass-spectrometric analyses; also, we are greatly indebted to Dr. D. G. Rea for his generous gift of the sample of octadeutero*cyclo*butane. This work was carried out whilst one of us (B. F. G.) was in receipt of a D.S.I.R. maintenance grant.

UNIVERSITY OF MANCHESTER. [*Received, October 26th*, 1955.]

* The derivation of this value has been critised by Seubold [5] but Dr. Seubold has agreed with us in personal correspondence that his criticism is invalid.

[4] Pritchard and Trotman-Dickenson, *Chem. and Ind.*, 1954, 1064.
[5] Seubold, *ibid.*, p. 1389.

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209. *Kinetic Studies in the Phosphinyl Chloride and Phosphorochloridate Series. Part V.* Evidence for a One-stage Mechanism in the Hydrolysis of Diethyl Phosphorochloridate.*

By I. DOSTROVSKY and M. HALMANN.

The hydrolysis of $(EtO)_2POCl$ in $H_2{}^{18}O$, and of $(EtO)_2P^{18}OCl$ in ordinary water, proceeds without oxygen exchange between the phosphoryl group and the water. A mechanism of rapid reversible intermediate formation is thus excluded. The probable mechanism is a one-stage bimolecular displacement.

THE kinetic study of solvolytic reactions of dialkyl phosphorochloridates [1] indicated a bimolecular mechanism and definitely excluded a unimolecular mechanism. Two forms of the bimolecular mechanism may be postulated: (1) a one-stage displacement, the approach of the nucleophilic reagent being simultaneous with the ejection of the chloride ion, and (2) rapid reversible formation of an intermediate complex which then slowly decomposes into the products. These forms are often indistinguishable by kinetics. It was considered probable that in the solvolysis of phosphonyl chlorides and phosphorochloridates quasi-phosphophonium compounds are involved.[2] In the solvolysis of dialkyl phosphorochloridates in absolute ethanol there is kinetic evidence that an intermediate complex mechanism does not contribute appreciably to the reaction. If a phosphorochloridate in solution in ethanol should first be in rapid equilibrium with a complex, which only slowly decomposes to the products:

$$(RO)_2POCl + EtOH \underset{\text{v. fast}}{\overset{\text{fast}}{\rightleftharpoons}} (RO)_2PCl(OH)(OEt) \overset{\text{slow}}{\rightleftharpoons} (RO)_2P(O)OEt + HCl$$

then a sample of, say, dimethyl phosphorochloridate dissolved in a large excess of ethanol should be converted almost completely into diethyl phosphorochloridate since the chances are about equal that in the reverse step not ethanol but methanol will be split off. The

* Part IV, *J.*, 1953, 516.

[1] Dostrovsky and Halmann, *J.*, 1953, 502, 516.
[2] Kosolapoff, "Organo-phosphorus Compounds," Wiley and Sons, New York, 1950, pp. 8, 138, 212.

rate of ethanolysis should then be the same as that of a sample of diethyl phosphorochloridate. In fact, considerable differences are found in the rate of ethanolysis of dimethyl, diethyl, di*iso*propyl, dibenzyl, and diphenyl phosphorochloridates.[1] Also, the products of ethanolysis are in each case different. A reaction sequence passing reversibly through an intermediate complex should produce mainly triethyl phosphate.

The present investigation * was undertaken in order to find out if in the hydrolysis of dialkyl phosphorochloridates the same one-stage mechanism obtains, or if some or all of the reaction passes through an intermediate complex. In a somewhat similar reaction, the hydrolysis of alkyl benzoates in aqueous dioxan, Bender [3] found that a considerable part of the hydrolysis probably involves reversible formation of an intermediate. In the Menschutkin reaction between methyl iodide and trimethylamine, Harman, Stewart, and Ruben [4] ruled out the reversible formation of an intermediate in which all the methyl groups are spatially equivalent. Methyl iodide labelled with tritium was caused to react with excess of inactive trimethylamine in ethanol or in benzene solution. The unchanged amine contained less than 0·1% of the tritium required for random distribution.

Diethyl phosphorochloridate was chosen as most convenient, since it is hydrolysed completely in water at room temperature within 1 min., according to the equation $(EtO)_2POCl + H_2O = (EtO)_2PO{\cdot}OH + HCl$; 2 equiv. of acid are found for each equiv. of chloride ion, and no hydrolysis of the ethyl groups takes place. In 70% aqueous dioxan at 0° the first-order rate constant for hydrolysis is $1{\cdot}4 \times 10^{-5}$ sec.$^{-1}$; the half-time is about 6 min. The diethyl hydrogen phosphate produced is very soluble in water and only very slightly soluble in *n*-hexane; therefore diethyl phosphorochloridate can be separated from the products by extraction with *n*-hexane. After partial hydrolysis of diethyl phosphorochloridate in heavy water (8·1 atom % excess of ^{18}O) and dioxan, the unchanged diethyl phosphorochloridate was extracted with *n*-hexane and analysed for ^{18}O. It had not become enriched (cf. p. 1006). Since the method of analysis involved hydrolysis of the extracted diethyl phosphorochloridate in ordinary water and ^{18}O determination in the resulting PO·OH group, it was considered possible that, if very fast and reversible exchange of oxygen between enriched water and the phosphorochloridate had occurred in the first stage, then all the ^{18}O gained by unhydrolysed phosphorochloridate would be lost in the second stage of hydrolysis in ordinary water. To check this, a number of experiments was made by a different method in which diethyl phosphorochloridate was hydrolysed completely, and the exchange of the phosphoryl oxygen with the water oxygen was determined after completion of the reaction.

TABLE 1. *Hydrolysis of diethyl phosphorochloridate* (f = atom % excess of ^{18}O).

	Reactants				f in excess H_2O:		
	$(EtO)_2POCl$		H_2O			Calc. for	
Run No.	mmoles	f	mmoles	f	Found	No exchange	Complete exchange
154	1·6	1·60	5·7	0·00	0·01	0·00	0·30
156	3·1	1·60	5·1	0·00	0·01	0·00	0·60
168	8·0	1·60	18·5	0·01	0·01	0·01	0·48
159	8·2	0·00	16·3	0·00	0·00	—	—
					f in PO·OH:		
188	0·38	1·60	55·9	0·00	0·82	0·80	0·01
201	1·15	0·00	37·1	3·86	1·80	1·93	3·74
214	1·37	0·00	18·5	5·52	2·72	2·76	5·14
219	1·65	0·00	15·9	5·64	2·88	2·82	5·10

In some experiments a small excess of ordinary water reacted with labelled phosphorochloridate (Table 1, Nos. 154, 156, 168); after completion of hydrolysis the excess of water was recovered by distillation: it had not become enriched appreciably in ^{18}O (Table 1, col. 6). If oxygen exchange had taken place during the reaction, the recovered

* A preliminary communication of part of this work was presented at the XIV International Congress of Pure and Applied Chemistry, Zürich, July 1955.

[3] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1628.
[4] Harman, Stewart, and Ruben, *ibid.*, 1942, **64**, 2294.

water should have become enriched in ^{18}O. For complete exchange, the required atom % excess of heavy oxygen is given in the last column of Table 1. The accuracy of these experiments is sufficient to decide that no more than 2% of the total reaction could have involved oxygen exchange. Incidentally, these results also prove that the product, diethyl hydrogen phosphate, does not exchange oxygen in aqueous solution at room temperature during several days.

No isotope effect on the rate of hydrolysis was observed (see Run 159). After reaction of ordinary diethyl phosphorochloridate with ordinary water, the excess of water was found to have remained unchanged in ^{18}O content. Thus diethyl phosphorochloridate does not differentiate between $H_2{}^{16}O$ and $H_2{}^{18}O$ within the experimental error.

In other experiments a large excess of water was used (Runs No. 175—219). In these cases it was evidently impossible to detect a considerable change in the ^{18}O content of the recovered excess of water because the change would be too small. Here, however, analysis of the ^{18}O enrichment in the PO·OH group of the resulting diethyl hydrogen phosphate can be used to detect oxygen exchange. A simple substitution of chlorine of the phosphorochloridate by hydroxyl must yield a PO·OH group in which the ^{18}O content per oxygen atom becomes the average of the ^{18}O contents of the original phosphoryl group and the water. It is assumed that in dilute aqueous solution the diethyl hydrogen phosphate is completely ionsied and the two oxygen atoms become equivalent. A mechanism in which the oxygen atoms of the phosphoryl group and of the water exchange completely should yield a PO·OH group in which the ^{18}O content becomes close to that of the water, which was in large excess. The calculated values for the excess of heavy oxygen in the PO·OH group are given in cols. 7 and 8 of Table 1 for the two extreme cases of reaction with no exchange and with complete exchange. As can be seen from col. 6, the experimental results are close to those required for hydrolysis without exchange.

The method of ^{18}O determination in the PO·OH of diethyl hydrogen phosphate was based on its reaction with di-*p*-tolylcarbodi-imide : [5]

$$2(EtO)_2PO{\cdot}OH + (p\text{-}MeC_6H_4{\cdot}N{:})_2C = (EtO)_2PO{\cdot}O{\cdot}PO(OEt)_2 + (p\text{-}MeC_6H_4{\cdot}NH)_2CO$$

The resulting di-*p*-tolylurea was isolated and decomposed at 320° in the presence of a catalyst to carbon dioxide, which was analysed by mass spectrometry for its ^{18}O content.

Run 188, between labelled diethyl phosphorochloridate and ordinary water, is of particular interest since it shows complete retention of the enriched oxygen of the phosphoryl group in spite of the large excess of ordinary water. In runs 201, 214, and 219, ordinary diethyl phosphorochloridate was caused to react with different proportions and concentrations of ^{18}O enriched water. In each case the PO·OH group of the resulting hydrogen phosphate contained half the excess of heavy oxygen of the original water.

The above results exclude a mechanism of rapid reversible formation of an intermediate in the hydrolysis of diethyl phosphorochloridate, and favour a simple one-stage displacement of the chlorine atom by water. An alternative to the one-stage displacement, indistinguishable experimentally, is slow formation of an intermediate, which breaks up immediately into the products.

Experimental

Materials.—Heavy oxygen-enriched water was obtained from the fractionating column of this laboratory.

$(Et^{18}O)_3P^{18}OCl$ was prepared by McCombie, Saunders, and Stacey's method : [6] To ^{18}O-labelled ethanol (6·2 g.) [7] and carbon tetrachloride (7 ml.) phosphorus trichloride (4 ml., freshly distilled) was added dropwise with stirring. Atmospheric moisture was excluded. The solution was refluxed for ½ hr. and dry nitrogen was then bubbled through for an hour. On distillation, 4·6 g. of diethyl hydrogen phosphite were obtained, b. p. 83—90°/20 mm. The product was dissolved in carbon tetrachloride, cooled in brine, and dry chlorine was passed through until a green colour developed. Dry nitrogen was then bubbled through the solution. On distillation,

[5] Khorana and Todd, *J.*, 1953, 2259; Khorana, *Chem. Rev.*, 1953, **53**, 145.
[6] McCombie, Saunders, and Stacey, *J.*, 1945, 380.
[7] Halmann and Samuel, *Bull. Res. Counc. Israel*, to be published.

4·6 g. of diethylphosphorochloridate were obtained, b. p. 78—81°/7 mm.; it was stored in a glass-stoppered flask in a desiccator.

Procedure.—(a) ***Partial hydrolysis.*** To a solution of ^{18}O-enriched water (8·10 atom % excess; 1·519 g.) in dioxan (3·5 ml.) in a thermostat at 0°, diethyl phosphorochloridate (1·5 ml.) was added. After 8 min. the mixture was extracted with *n*-hexane (6 ml.), a syringe being used as separatory funnel. The hexane layer was washed with distilled water (2 × 2 ml.) and the solvent was removed by evaporation under reduced pressure. The residual oil was dissolved in distilled water (1 ml.), and after 5 min. was dried at 0·05 mm. The ^{18}O content of the resulting diethyl hydrogen phosphate was determined by the carbodi-imide method.[a] and was found to be equal to that of natural water within ±2%. The extent of exchange during hydrolysis must therefore be less than 0·1% of that calculated for complete equilibration.

(b) ***Complete hydrolysis.*** Reactions were carried out in 10-ml. flasks with TS 10/30 inner joints fitted with similar outer stoppers. The phosphorochloridate and the water were weighed into the flask and mixed. When hydrolysis was complete, the excess of water was distilled at room temperature in a vacuum still. The apparatus consisted of a three-way stopcock, one limb of which was connected to a vacuum line (20 microns). The other limbs were fitted with TS 10/30 outer joints. To one of these the reaction flask was connected, and to the other a similar empty flask. The reaction flask was cooled in liquid nitrogen and both flasks were evacuated. The stopcock was then turned to connect only the two flasks, and Dewar flask containing liquid nitrogen was transferred to the empty flask. After most of the water had distilled over, the reaction flask was connected to the vacuum line in order to remove residual water from the diethyl hydrogen phosphate, which was then analysed for ^{18}O by the carbodi-imide method. A sample of the distillate was equilibrated with a small amount of ordinary carbon dioxide in a sealed bulb and was assayed by mass spectrometer for its ^{18}O enrichment; at the same time a sample of the water initially used in the reaction was analysed.

The authors are indebted to Dr. F. S. Klein and Mr. M. Feld for the mass-spectrometric determinations.

Isotope Department,
The Weizmann Institute of Science, Rehovoth, Israel. [*Received, November 7th*, 1955.]

[a] Halmann, *J.*, to be published.

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210. *Infrared Spectra of Natural Products. Part V.* The Characterisation of Carbonyl Groups in Pentacyclic Triterpenoids.*

By A. R. H. Cole and D. W. Thornton.

The carbonyl frequencies of a large number of pentacyclic triterpenoids based on oleanane, lupane, and ursane have been measured in carbon tetrachloride and chloroform, and characteristic frequencies for 18 types of carbonyl function are given. Some six-membered ring ketones cannot be distinguished by carbonyl absorption alone, but bands due to bending vibrations of adjacent methylene groups assist in their characterisation.

The use of infrared spectra has proved valuable in solving problems of steroid structure, and the results obtained in that field have been summarised by R. N. Jones and Herling [1] and by Cole.[2] Compounds containing fused *cyclo*hexane systems are particularly suitable for infrared work since a very large number of compounds are available based on a fairly constant molecular skeleton, and differing mainly in the number and positions of substituents. Furthermore, these compounds being for the most part saturated and relatively non-polar, electronic effects are rarely transferred beyond neighbouring carbon atoms, and the change in spectrum brought about by altering a particular substituent can usually be predicted fairly accurately.

Recently emphasis in this type of structural chemistry has shifted from steroids to

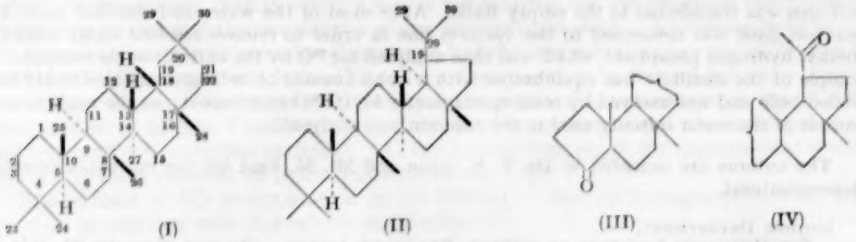
* Part IV, *J.*, 1955, 2624.

[1] R. N. Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252.
[2] Cole, *Rev. Pure Appl. Chem.* (*Australia*), 1954, **4**, 111.

triterpenoids, and it has been usual to apply steroid infrared results to the latter compounds. While in many cases this practice has given valuable information, it would be preferable to know the infrared frequencies for groups in triterpenoid molecules themselves, since the environments at each substituent position are not identical in the two types of ring system. For instance, the presence of the $C_{(4)}$-*gem*-dimethyl group might well influence a $C_{(3)}$-substituent, and the amount of strain in ring C which is fused to two six-membered rings in the pentacyclic triterpenoids will be considerably different from that in the steroids where the adjacent D-ring is five-membered. Also the large number of angular methyl groups will alter the appearance of the spectra, especially in the regions of C–H stretching and bending absorption.

In this paper carbonyl groups in the pentacyclic triterpenoids are considered and it is hoped later to present results covering ethylenic double bonds, hydroxyl groups, C–H groups, carboxylic acids and their methyl esters, and some aspects of stereochemistry. Similar results for many tetracyclic triterpenoids will also be given later.

The compounds considered below are derivatives of oleanane (I), lupane (II), and ursane. There is still some doubt about the structure of the last hydrocarbon [3] but the numbered positions of carbonyl groups are the same as in the oleanane and lupane series.



(I) (II) (III) (IV)

The types of carbonyl group encountered include cyclic ketones at positions 3, 11, 12, and 19, carboxylic acids and their methyl esters, aldehydes, lactones, acetates, formates benzoates, and various conjugated ketones. Other possible types are the A-trisnor-$C_{(3)}$-ketone (III) formed from 3β-hydroxy-compounds by dehydration with phosphorus pentachloride and subsequent oxidation, and the methyl ketone (IV) from lupeol by oxidation of the side chain.

Primarily, the absorption due to the carbonyl stretching vibration is used to distinguish between these types, but certain ambiguities exist in that region. Therefore absorption bands in other regions which are useful in identifying certain groups are also given below.

Experimental

The infrared spectrometer employed in this work consists of a Grubb-Parsons S.3.A. monochromator used in conjunction with a Perkin–Elmer thermocouple, light chopper, and No. 81 amplifier. A calcium fluoride prism is used for all measurements between 1300 and 3800 cm.$^{-1}$ and a double-pass sodium chloride system [4] between 670 and 1300 cm.$^{-1}$. The instrument was calibrated by using data summarised by Downie, Magoon, Purcell, and Crawford,[5] and band positions can be measured with an accuracy of $\pm 0{\cdot}5$ cm.$^{-1}$ between 1300 and 1900 cm.$^{-1}$. The spectrometer is controlled by thermostat at 30° $\pm$ 0·5° and the air inside the case is continuously circulated through a Burnett and Lewis " Humidryer " to reduce the amount of atmospheric water vapour absorption. A string-type automatic slit drive [6] was employed to compensate for the fall-off in energy of the source.

All compounds were studied as dilute solutions (approximately 0·01M) to minimise the effects

[3] Cf. Jeger, *Fortschr. Chem. org. Naturstoffe*, 1950, **7**, 47; Corey and Ursprung, *Chem. and Ind.*, 1954, 1387; Beton and Halsall, *ibid.*, p. 1560; Allan, Beaton, Shaw, Spring, Stevenson, Stewart, and Strachan, *ibid.*, 1955, 281.

[4] Walsh, *Nature*, 1951, **167**, 810; Rochester and Martin, *Nature*, 1951, **168**, 785.

[5] Downie, Magoon, Purcell, and Crawford, *J. Opt. Soc. Amer.*, 1953, **43**, 941.

[6] Blount and Cole, *J. Sci. Inst.*, 1955, **32**, 471.

of intermolecular interaction. The advisability of using dilute solutions instead of solid samples for this type of work has often been stressed.[7]

Most triterpenoids are sufficiently soluble in carbon tetrachloride to permit that solvent to be used in cells of about 1 mm. thickness, but for dihydroxy-compounds or carboxylic acids it is necessary to use cells 3 mm., and occasionally up to 10 mm., in thickness. Since many natural products are more soluble in chloroform, representative compounds have also been studied in this solvent. However, if the sample is sufficiently soluble, carbon tetrachloride is much to be preferred since the same solution may be used for studying the regions of C–H absorption which are obscured by chloroform absorption. Moreover chloroform, as usually supplied, contains a small amount of ethanol to inhibit oxidation to carbonyl chloride and, while this does not affect its use as a solvent in the carbonyl region, it must, of course, be removed if the same solution is to be used for the study of hydroxyl absorption. This may be done in small batches by pouring the chloroform through silica gel prepared by heating it at 140° under vacuum. Alcohol-free chloroform prepared in this manner will keep for about 1 week, oxidation being readily detected by the appearance of carbonyl absorption at 1810 cm.$^{-1}$.

The absorption in the regions of C–H (2800—3100 cm.$^{-1}$) and C=O (1650—1800 cm.$^{-1}$) stretching vibrations is between two and three times as intense as that in the C–H bending region (1350—1500 cm.$^{-1}$). We have found it convenient to weigh out only one solution containing about 5 mg. per ml. (~0·01M) and to use a 1·3 mm. cell for the former regions and a 3·3 mm. cell for the latter and also for the O–H stretching (~3630 cm.$^{-1}$) and C=C stretching (1570—1680 cm.$^{-1}$) regions.

Results and Discussion

The carbonyl frequencies of individual compounds are given in Tables 1 and 2 while the average values for the various types are summarised in Table 3. These Tables and Table 4 include the frequencies of other bands which may be used to distinguish or confirm doubtful types of carbonyl group. The values given in Table 3 are based on compounds listed under *A* in Tables 1 and 2, and it must be remembered that the frequency ranges might be wider when the particular absorption band is overlapped by that due to another group.

With the exception of the carboxylic acids, which are complicated by hydrogen bonding, the carbonyl frequencies are always lower (and the bands slightly broader) in chloroform solution than in carbon tetrachloride, the mean difference varying from 3 cm.$^{-1}$ for the $C_{(11)}$-ketones to 20 cm.$^{-1}$ for the γ-lactones. The greater part of the following discussion is based on the results for carbon tetrachloride. Although carbon disulphide has not been used in this work its solutions are known to give approximately the same absorption frequencies as carbon tetrachloride.

The various types listed in Table 3 fall into a number of groups which cannot be identified unequivocally by the carbonyl frequency alone. Such a group includes aldehydes, acetates, formates, and methyl esters which all absorb between 1723 and 1737 cm.$^{-1}$. The presence of these will sometimes be known from the chemistry of the compound but in any case they often can be distinguished from one another by observing bands in other regions. For example, acetates absorb [8] at 1240 cm.$^{-1}$ and [9] at 1375 and 1368 cm.$^{-1}$. Methyl esters have characteristic bands [9] near 1438, at [10] 1135 and 1155, and near 760—790 cm.$^{-1}$ while formates absorb at 1176 cm.$^{-1}$.

The benzoate frequency (1719 cm.$^{-1}$) is relatively unambiguous but, if necessary, confirmation of its presence can be obtained from the strong bands [1] at 1273 and 710 cm.$^{-1}$. It should be noted that, if it is necessary to esterify a hydroxyl group before carrying out a reaction, or in order to facilitate chromatography, and if subsequently infrared measurements are to be made, it is preferable to use acetates of compounds containing six-membered ring carbonyl groups and benzoates of those containing five-membered ring carbonyls. In this way, the interference of the ester carbonyl absorption with that of the group being studied is kept at a minimum.

[7] Jones and Dobriner, *Vitamins and Hormones*, 1949, **7**, 293; Cole, *Chem. and Ind.*, 1954, 661; Dickson, Page, and Rogers, *J.*, 1955, **443**.
[8] Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1951, **73**, 3215.
[9] Jones and Cole, *ibid.*, 1952, **74**, 5648.
[10] Cole and Thornton, unpublished results.

TABLE 1. *Non-conjugated carbonyl frequencies* (*cm.*$^{-1}$).

In each section, compounds without completely overlapping carbonyl absorption in carbon tetrachloride solution are given under *A* and those in which bands are not resolved, under *B*. Because of frequency shifts and band broadening in chloroform solution some bands of compounds listed under *A* might not be completely resolved in this solvent. Compounds given under 1*C* and 12*C* show interaction effects which are discussed in the text.

CCl_4 soln.	Compound	$CHCl_3$ soln.	Ester C=O [a]	Adjacent-CH_2 [b]
	1 *A γ-Lactones*			
1772	3β : 13β-Dihydroxyursan-28-oic 13(28)-lactone (ursolic acid lactone)	1754	—	—
1773	3β : 13β-Dihydroxy-18α-oleanan-28-oic 13(28)-lactone	1755	—	—
1774	3β-Acetoxy-13β-hydroxyoleanan-28-oic 13(28)-lactone *	1754	—	—
1774	3β-Acetoxy-13β-hydroxy-18α-oleanan-28-oic 13(28)-lactone *	1756	—	—
1775	3β : 13β-Dihydroxyoleanan-28-oic 13(28)-lactone (oleanolic acid lactone)	1751	—	—
	1 *C*			
1782	3β : 12α-Diacetoxy-13β-hydroxyoleanan-28-oic 13(28)-lactone *	1766	—	—
1779	12α-Bromo-3β : 13β-dihydroxyoleanan-28-oic 13(28)-lactone	1763	—	—
1779	3β-Acetoxy-12α : 13β-dihydroxyoleanan-28-oic 13(28)-lactone *	1760	—	—
1791	3β-Acetoxy-13β-hydroxy-12-oxo-oleanan-28-oic 13(28)-lactone *	1772	—	—
	2 *A Five-membered ring ketone*			
1740	Methyl 3-oxo-A-trisnorlupan-28-oate * [c]	—	—	1413
	3 *A Acetates*			
1732	Urs-12-en-3β-yl acetate (α-amyrin acetate)	—	—	—
1732	Lup-20(29)-en-3β-yl acetate (lupenyl acetate)	1719	—	—
1732	3β-Acetoxylup-20(29)-en-30-al *	1718	—	—
1732	3β-Acetoxy-13β-hydroxy-12-oxo-oleanan-28-oic 13(28)-lactone *	1722	—	—
1733	3β-Acetoxyurs-12-en-11-one *	1717	—	—
1733	3β : 12α-Diacetoxy-13β-hydroxyoleanan-28-oic 13(28)-lactone *	1725	—	—
1733	3β-Acetoxy-12α : 13β-dihydroxyoleanan-28-oic 13(28)-lactone *	1722	—	—
1734	3β-Acetoxy-13β-hydroxyoleanan-28-oic 13(28)-lactone *	1721	—	—
1734	3β-Acetoxy-13β-hydroxy-18α-oleanan-28-oic 13(28)-lactone *	1721	—	—
1735	3β-Acetoxyoleanan-12-one *	1721	—	—
1737	3β : 28-Diacetoxyoleanan-19-one *	—	—	—
	3 *C*			
1747	3β : 12α-Diacetoxy-13β-hydroxyolcanan-28-oic 13(28)-lactone *	1741	—	—
	4 *B* Aldehyde			
1732	3β-Acetoxyolean-18-en-28-al	—	—	—
	5 *A Methyl esters*			
1723	Methyl 3β : 19α-dihydroxy-12-oxo-oleanan-28-oate *	1714	—	—
1725	Methyl 3-oxours-12-en-28-oate *	1714	—	—
1725	Methyl urs-12-en-28-oate	—	—	—
1725	Methyl 3β-hydroxy-12-oxo-oleanan-28-oate *	1715	—	—
1726	Methyl 3β-hydroxyurs-12-en-28-oate (methyl ursolate)	—	—	—
1726	Methyl 3-oxo-olean-18-en-28-oate *	1716	—	—
1727	Methyl 3β-hydroxyolean-18-en-28-oate (methyl morolate)	—	—	—
1727	Methyl 3β : 19α-dihydroxyolean-12-en-28-oate (methyl siaresinolate)	—	—	—
1728	Methyl 3-oxolupan-28-oate *	1719	—	—
1729	Methyl 3β-hydroxyolean-12-en-28-oate (methyl oleanolate)	—	—	—
1729	Methyl 3β-hydroxylup-20(29)-en-28-oate (methyl betulate)	—	—	—
1730	Methyl lupan-28-oate	—	—	—
1730	Methyl 3-oxo-A-trisnorlupan-28-oate * [c]	—	—	—
1731	Methyl 3 : 19-dioxo-olean-13(18)-en-28-oate *	1721	—	—
1732	Methyl 3 : 12 : 19-trioxo-olean-13(18)-en-28-oate *	1725	—	—
1733	Methyl 3 : 19-dioxo-olean-12-en-28-oate *	1721	—	—
	6 *A Formates*			
1723	*allo*Betulin formate	1714	—	—
1726	Olean-18-en-3β : 28-diol diformate	1714	—	—
	7 *A Benzoates*			
1717	3β-Benzoyloxylup-20(29)-en-30-al *	1707	—	—
1719	3β-Benzoyloxyoleanan-12-one *	1708	—	—
1720	Urs-12-en-3β-yl benzoate (α-amyrin benzoate)	—	—	—
1720	Olean-12-en-3β-yl benzoate (β-amyrin benzoate)	—	—	—

TABLE 1. (*Continued.*)

CCl_4 soln.	Compound	$CHCl_3$ soln.	Ester C=O [a]	Adjacent-CH_2 [b]
	7 B			
1721	Methyl 3β-benzoyloxyolean-18-en-28-oate	—	—	—
	8 A $C_{(19)}$-*Ketone*			
1712	3β : 28-Diacetoxyoleanan-19-one [a]	not resolved	—	—
	8 B			
1705	Methyl 3β-acetoxy-12 : 19-dioxo-oleanan-28-oate [a]	1695	1730 (1721)	—
1708	Methyl 3 : 19-dioxo-olean-12-en-28-oate [a]	1703	—	—
1715	Methyl 3β-acetoxy-19-oxo-olean-28-oate [a]	1714	1730 (1714)	—
1717	Methyl 3β-acetoxy-19-oxo-18α-olean-12-en-28-oate [a]	1714	1735 (1721)	—
1720	Methyl 3β-acetoxy-19-oxo-18α-oleanan-28-oate [a]	—	1738	—
	9 A 30-nor-$C_{(30)}$-*ketone*			
1712	3β-Hydroxy-30-norlupan-20-one	1700	—	1354 [d]
	10 A $C_{(3)}$-*Ketones*			
1706	Urs-12-en-3-one	1698	—	1430 [c]
1707	Methyl 3-oxours-12-en-28-oate [a]	1698	—	—
1707	Urs-12-en-3 : 11-dione [a] [e]	—	—	1428
1708	Methyl 3-oxolupan-28-oate [a]	1699	—	—
1708	Methyl 3-oxo-olean-18-en-28-oate [a]	1700	—	—
1708	28-Norolean-17-en-3-one	1698	—	1431
1708	Phyllanth-3-one [f]	1699	—	1427
1709	Methyl 3 : 19-dioxo-olean-13(18)-en-28-oate [a]	1698	—	—
	10 B			
1708	Methyl 3 : 19-dioxo-olean-12-en-28-oate [a]	1703	—	—
1709	Methyl 3 : 12 : 19-trioxo-olean-13(18)-en-28-oate [a]	1698	—	—
	11 A $C_{(11)}$-*Ketones*			
1706	Methyl 3β-acetoxy-11-oxo-oleanan-28-oate [a]	1703	1727 (1715)	—
1707	Ursan-11-one [c]	—	—	1430 [c]
	12 A $C_{(12)}$-*Ketones*			
1698	Methyl 3β : 19α-dihydroxy-12-oxo-oleanan-28-oate [a]	1692	—	—
1699	Methyl 3β-acetoxy-19α-hydroxy-12-oxo-oleanan-28-oate [a]	1692	1725 (1714)	1422 [c]
1700	3β-Hydroxyoleanan-12-one	1692	—	1420
1701	3β-Acetoxyoleanan-12-one [a]	1692	—	1420
1701	3β-Benzoyloxyoleanan-12-one [a]	1696	—	1419
1701	Methyl 3β-hydroxy-12-oxo-oleanan-28-oate [a]	1696	—	1419
1703	Methyl 3β-acetoxy-12-oxo-oleanan-28-oate [a]	1696	1727 (1717)	1420
	12 B			
1705	Methyl 3β-acetoxy-12 : 19-dioxo-oleanan-28-oate [a]	1695	1730 (1721)	1415
	12 C			
1718	3β-Acetoxy-13β-hydroxy-12-oxo-oleanan-28-oic 13(28)-lactone [a]	1715	—	1426
	13 A Carboxylic acids			
1744 [g] / 1687	3β-Hydroxyurs-12-en-28-oic acid (ursolic acid)	1714	—	—
1742 [g] / 1696	3β-Hydroxyolean-18-en-28-oic acid (morolic acid)	1714	—	—
1745 [g] / 1696	3β-Hydroxyolean-12-en-28-oic acid (oleanolic acid)	1714	—	—

[a] These compounds have one or more additional carbonyl bands, the frequencies of which are given in other sections.

[b] Composite bands of methyl ester and acetate carbonyl groups which are not given in sections 3 and 5 (value for chloroform solution in parentheses). [c] Carbon tetrachloride solution. [d] Prepared in this department. [e] Methyl absorption of $-CO\cdot CH_3$ group. [f] Partly-resolved shoulder only. [g] Hexacyclic triterpenoid, included because of close relation to α-amyrin series. [h] Monomer frequency —see text.

The six-membered ring ketones at positions 3, 11, 12, and 19 and the 30-nor-$C_{(30)}$-ketone (IV) which absorb between 1698 and 1712 cm.$^{-1}$ cannot all be distinguished with certainty, but a study of the region of C–H bending absorption will usually allow a distinction to be made (see below). By careful measurements a $C_{(12)}$-ketone group can be distinguished from the others, but if only a sodium chloride prism is available this might not be possible.

TABLE 2.† *Conjugated carbonyl frequencies (cm.$^{-1}$).*

CCl_4 soln.	Compound	$CHCl_3$ soln.	Ester C=O.
	14 *A* $\Delta^{20(29)}$-$C_{(30)}$-*aldehydes*		
1696	3β-Acetoxylup-20(29)-en-30-al *	1689	—
1696	3β-Benzoyloxylup-20(29)-en-30-al *	1691	—
	15 *A* $\Delta^{13(18)}$-$C_{(12)}$: $C_{(19)}$-*Diketone*		
1692, 1709	Methyl 3 : 12 : 19-trioxo-olean-13(18)-en-28-oate *	—	—
	16 *A* $\Delta^{13(18)}$-$C_{(19)}$-*Ketone*		
1689	Methyl 3 : 19-dioxo-olean-13(18)-en-28-oate *	1684	—
	17 *A* Δ^{12}-$C_{(11)}$-*Ketones*		
1665	Methyl 3β-acetoxy-11-oxo-olean-12-en-28-oate *	1649	1729 (1721)
1665	Methyl 3β-acetoxy-11-oxours-12-en-28-oate *	1656	1731 (1721)
1665	Methyl 3β-acetoxy-11-oxo-olean-12-en-29-oate *	1652	1731 (1721)
1665	Methyl 3β-acetoxy-11-oxo-18α-olean-12-en-28-oate *	1656	1734 (1721)
1666	Urs-12-en-11-one *	1650	—
1666	Urs-12-en-3 : 11-dione * *	—	—
1666	3β-Acetoxyurs-12-en-11-one *	1649	—
	18 *A* $\Delta^{12:18}$-*Diene*-$C_{(11)}$-*ketone*		
1663	Methyl 3β-acetoxy-11-oxo-oleana-12 : 18-dien-28-oate *	1649	1732 (1719)

† See heading and footnotes to Table 1.

TABLE 3. *Summary of carbonyl frequencies (cm.$^{-1}$).*

CCl_4 soln. Mean	CCl_4 soln. Range		$CHCl_3$ soln. Mean	$CHCl_3$ soln. Range
1774 (5) †	1772—1775	γ-Lactone	1754 (5)	1751—1756
1740 (1)	—	A-Tris-nor-$C_{(3)}$-ketone (five-membered ring)	—	—
1733 (11)	1732—1737	Acetate	1721 (9)	1717—1725
1732 (1)	—	Aldehyde	—	—
1728 (16)	1723—1733	Methyl ester	1718 (8)	1714—1725
1725 (2)	1723—1726	Formate	1714 (2)	—
1719 (4)	1717—1720	Benzoate	1708 (2)	1707—1708
1712 (1)	—	$C_{(19)}$-Ketone (oleanane series)	—	—
1712 (1)	—	$C_{(30)}$-Ketone (30-norlupane series)	1700 (1)	—
1708 (8)	1706—1709	$C_{(3)}$-Ketone	1699 (7)	1698—1700
1706 (2)	1706—1707	$C_{(11)}$-Ketone	1703 (1)	—
1700 (7)	1698—1703	$C_{(12)}$-Ketone	1694 (7)	1692—1696
1744, 1693 (3)	1742—1745, 1687—1696	Carboxylic acid	1714 (3)	—
1696 (2)	—	Conjugated aldehyde	1690 (2)	1689—1691
1709, 1692 (1)		$\Delta^{13(18)}$-$C_{(12)}$: $C_{(19)}$-Diketone (oleanane series)	—	—
1689 (1)	—	$\Delta^{13(18)}$-$C_{(19)}$-Ketone (oleanane series)	1684 (1)	—
1665 (7)	1665—1666	Δ^{12}-$C_{(11)}$-Ketone	1652 (6)	1649—1656
1663 (1)	—	$\Delta^{12:18}$-Diene-$C_{(11)}$-ketone	1649 (1)	—

† No. of compounds studied.

TABLE 4. *Frequencies of "adjacent methyl or methylene" groups (cm.$^{-1}$, in carbon tetrachloride solutions).*

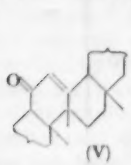
	Mean	Range
$C_{(11)}$-Ketone	1430 (1) †	—
$C_{(3)}$-Ketone	1429 (4)	1427—1431
$C_{(12)}$-Ketone	1420 (6)	1419—1422
A-Nor-$C_{(3)}$-ketone	1413 (1)	—
30-Nor-$C_{(30)}$-ketone	1354 (1)	—

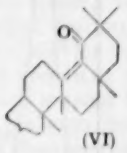
† No. compounds of studied.

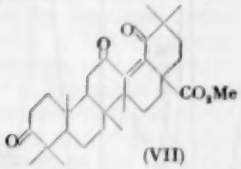
The frequency of 1712 cm.$^{-1}$ for the $C_{(19)}$-ketone should be regarded as a tentative assignment only, since in all compounds available the absorption of this group was overlapped to some extent by neighbouring bands.

The carboxylic acids exist in carbon tetrachloride solution mostly in the dimeric form with the carboxyl groups hydrogen-bonded, and this system absorbs near 1693 cm.$^{-1}$. The small amount of monomer present has its carbonyl frequency at 1744 cm.$^{-1}$ which usually appears as a weak shoulder at the side of the dimer absorption. The acids are anomalous in chloroform solution where their carbonyl bands are extremely broad with the peak near 1714 cm.$^{-1}$ This broadening must be related to solvent–solute hydrogen bonding, and further work on these compounds is in progress.

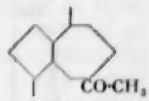
The well-known lowering of carbonyl frequency (which is accompanied by an increase in intensity) with conjugation is clearly illustrated by the triterpenoids listed in Table 2. The drop in frequency from that of the saturated compound is proportional to the efficiency of the conjugation but the effect may be opposed to some extent by the stiffening of the ring system caused by the introduction of the double bonds. Thus the lowering is much greater in the Δ^{12}-$C_{(11)}$-ketones (V; 41 cm.$^{-1}$) than in the $\Delta^{13(18)}C_{(19)}$-ketone (VI; 23 cm.$^{-1}$).


(V)


(VI)



(VII)



(VIII)

In the only $\Delta^{13(18)}$-$C_{(12)}$: $C_{(19)}$-diketone (VII) studied neither carbonyl group conjugates completely with the double bond. The total carbonyl absorption consists of bands at 1732 (ester), 1709, and 1692 cm.$^{-1}$, with the middle peak approximately twice as intense as the other two. Part of this intensity belongs to the $C_{(3)}$-ketone while the rest of it and the band at 1692 cm.$^{-1}$ must be due to the components of the conjugated system.

With the exception of some 13(28)-lactones with $C_{(12)}$-substituents all the polycarbonyl compounds studied absorb at the same frequencies as the respective monocarbonyl compounds, and the bands are resolved if they differ in frequency by about 10 cm.$^{-1}$. When their centres are closer than this they appear as one band, which may or may not be asymmetrical, and intensity measurements [11] must be used to determine the number of groups present.

Interaction of Groups.—The overlapping of independent absorption bands should not be confused with interaction of neighbouring groups which causes them to absorb at frequencies displaced from their normal positions. A number of lactones listed in Table 1 (1*C*) show this type of interaction. Thus 3β-acetoxy-12-oxo-oleanolic lactone, which might be expected to absorb at 1774 (lactone), 1732 (acetate), and 1700 cm.$^{-1}$ ($C_{(12)}$-ketone), has its carbonyl bands at 1791, 1732, and 1718 cm.$^{-1}$. A hydroxy- or bromo-substituent at $C_{(12)}$ raises the lactone carbonyl frequency to 1779 cm.$^{-1}$. The spectrum of 3β : 12α-diacetoxy-oleanolic lactone illustrates the differentiation of two types of acetate group, since the $C_{(12)}$-acetoxy-carbonyl frequency is raised to 1747 cm.$^{-1}$ while the $C_{(3)}$-acetate absorbs at the expected position (1733 cm.$^{-1}$). The lactone absorption is at 1782 cm.$^{-1}$.

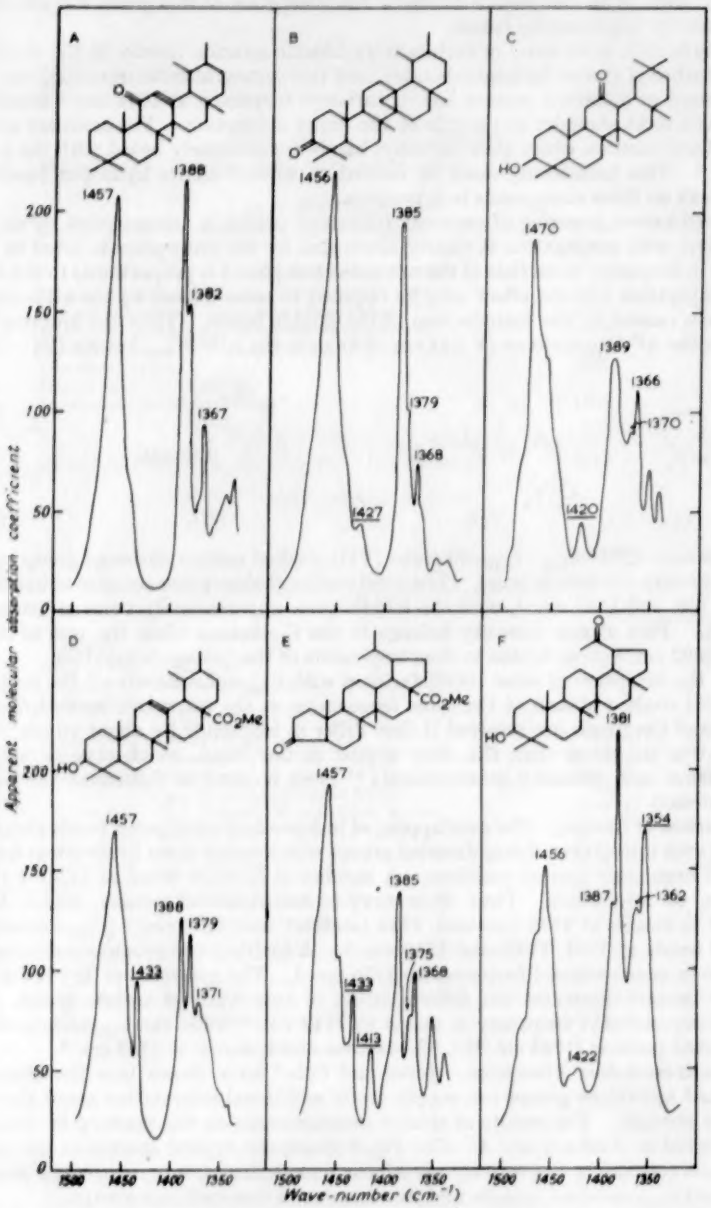
Adjacent-methylene Absorption.—Jones and Cole [9] have shown how the absorption of methyl and methylene groups can supply useful additional information about the carbonyl groups in steroids. The results of similar measurements on the pentacyclic triterpenoids are presented in Tables 1 and 4. The Fig. * illustrates typical spectra in this region for compounds containing respectively no adjacent methylene group, methylene groups next to $C_{(3)}$- and $C_{(12)}$-carbonyl groups, and five-membered ring carbonyl groups.

The effect of a carbonyl group is to lower the bending frequency of an adjacent methyl or methylene group. It should be noted particularly that the effects in the triterpenoids

* Formulæ based on ursane in the figure are shown with the usual six-membered E-ring, but are not intended to support this structure rather than another (see above).

[11] Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72; Jones, Ramsay, Keir, and Dobriner, *ibid.*, p. 80.

Infrared spectra in the region of methyl and methylene bending absorption.



A. Urs-12-en-11-one.
B. Phyllanth-3-one.
C. 3β-Hydroxyoleanan-12-one.
D. Methyl 3β-hydroxyurs-12-en-28-oate (methyl ursolate).
E. Methyl 3-oxo-A-trisnorlupan-28-oate.
F. 3β-Hydroxy-30-norlupan-20-one.

are not identical with those found in steroid spectra for comparable positions. In steroids, $C_{(2)}$- and $C_{(4)}$-methylene groups ($C_{(3)}$-ketone) absorb near 1420 cm.$^{-1}$ while in the 3-oxotriterpenoids the $C_{(2)}$-methylene group absorbs near 1430 cm.$^{-1}$; a $C_{(11)}$-methylene in 12-oxosteroids absorbs at 1434 cm.$^{-1}$ while the same group in 12-oxotriterpenoids absorbs close to 1420 cm.$^{-1}$. The only five-membered ring ketone studied here, an A-nor-$C_{(3)}$-ketone (III), has its adjacent methylene absorption at 1413 cm.$^{-1}$, which is close to the range found for 17-oxosteroids and tetracyclic triterpenoids.[12]

The absorption in this region of the spectrum is slightly complicated by the fact that methyl esters have a band near 1435 cm.$^{-1}$ (see Fig.; D) and this will interfere with measurements on $C_{(3)}$-ketones. However, the carbonyl frequencies of these two types are easily distinguished. $C_{(12)}$-Ketones and those on five-membered rings may be positively identified even in the presence of methyl esters (see Fig.; E). This is important particularly when dealing with five-membered ring ketones, whose carbonyl absorption is very close to that of esters and may not be resolved, expecially if a sodium chloride prism is used. The $C_{(19)}$-ketones (oleanane series) have no adjacent methylene groups.

The methyl ketone (IV) prepared from lupeol may be identified by the well-defined band at 1354 cm.$^{-1}$ due to the bending vibration of the side-chain methyl group (see Fig.; F). The carbonyl and methyl bending frequencies of this compound are similar to those described by Jones and Cole [9] for the 20-oxosteroids of the pregnane series, except that an additional small band is present at 1422 cm.$^{-1}$. This might be due to the antisymmetrical methyl bending vibration lowered by the influence of the carbonyl group from its usual position near 1450 cm.$^{-1}$ (always obscured by ring methylene absorption) but such an effect was not found in the 20-oxosteroids. However, in the sesquiterpene field the methyl ketone (VIII) prepared from guaiol [13] shows, besides its carbonyl band at 1712 and " adjacent methyl " band at 1352 cm.$^{-1}$, a small band at 1426 cm.$^{-1}$ similar to that described above for the lupeol derivative.

The infrared spectrometer was purchased through a generous grant from the Nuffield Foundation, to whom one of the authors (A. R. H. C.) is also indebted for a Fellowship. They are also grateful to Professor D. H. R. Barton, F.R.S., who supplied nearly all the compounds, to Dr. D. E. White, Miss K. J. L. Thieberg, and Messrs. T. H. N. Newton and B. J. Parkes who prepared the remaining samples, and to Mr. E. L. Blount who constructed parts of the apparatus.

THE UNIVERSITY OF WESTERN AUSTRALIA,
NEDLANDS, WESTERN AUSTRALIA. [*Received, August 29th*, 1955.]

[12] Barnes, Barton, Cole, Fawcett, and Thomas, *J.*, 1953, 571.
[13] Cole, Melrose, and White, unpublished results.

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211. *Allenes. Part I. The Rearrangement of Prop-2-ynyl Acetates.*

By PHYLLIS D. LANDOR and S. R. LANDOR.

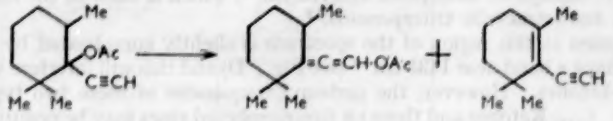
The pyrolysis of 1-ethynyl-2 : 2 : 6-trimethyl*cyclo*hexyl acetate has been shown to give the allene, 2 : 2 : 6-trimethyl*cyclo*hexylidenevinyl acetate, besides the 1-ethynyl-2 : 2 : 6-trimethyl*cyclo*hexene previously isolated. In the tetramethyl series the allenic acetate was isolated as the sole product in high yield. The mechanism of this rearrangement is discussed. Hydrolysis of the allenic acetates gave unsaturated aldehydes.

THE work described in this paper originated in the discovery that one of the main products from the pyrolysis of 1-ethynyl-2 : 2 : 6-trimethyl*cyclo*hexyl acetate [1] (I) was the allenic acetate (II) while 1-ethynyl-2 : 2 : 6-trimethyl*cyclo*hexene (III) was formed at the same time in smaller yield.

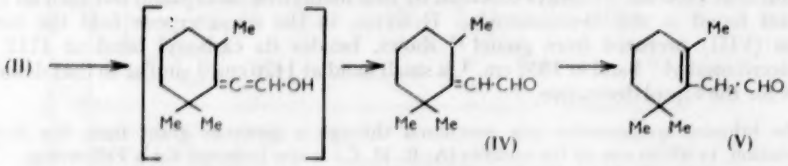
The *cyclo*hexene (III), required by us for other purposes, was prepared by pyrolysis from the crystalline acetate (I) (free from hydroxylic impurities as shown by its infrared

[1] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.

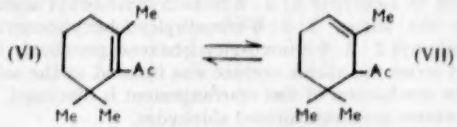
spectrum); it formed a lower-boiling fraction: the higher-boiling fraction had a fruity odour distinct from the typical acetylenic odour of the starting material and was isomeric with the latter. The higher-boiling material gave no ultraviolet absorption maximum, so the presence of a conjugated chromophore such as the enyne system in (III) was excluded; its infrared spectrum contained no acetylenic C–H stretching band near 3300



cm.$^{-1}$, but a strong C=O stretching band at 1750 cm.$^{-1}$ indicating the acetate group (original acetate band at 1745 cm.$^{-1}$) and a strong allene C=C stretching band at 1970 cm.$^{-1}$. This evidence strongly suggested the allenic structure (II). Adding the 2 : 4-dinitrophenylhydrazine reagent to the allenic acetate (II) gave, within a few seconds, vermilion needles which had the characteristic ultraviolet absorption bands expected from the 2 : 4-dinitrophenylhydrazone of a conjugated, unsaturated carbonyl compound.[2,3] The acetate (II) was apparently hydrolysed, under the acid conditions used, to 2 : 2 : 6-trimethyl*cyclo*hexylideneacetaldehyde (IV) which immediately gave the 2 : 4-dinitrophenylhydrazone.



A compound described by Henbest and Woods[4] as the 2 : 4-dinitrophenylhydrazone of (IV) but differing substantially in melting point and light absorption from our derivative had been obtained from a by-product in the formic acid isomerisation of 1-ethynyl-2 : 2 : 6-trimethyl*cyclo*hexanol; the free aldehyde had not been isolated, the main product being 1-acetyl-2 : 2 : 6-trimethyl*cyclo*hexene (VI). In our hands the product obtained by this method (as used by Henbest and Woods or under varying conditions) did not yield the vermilion 2 : 4-dinitrophenylhydrazone, but very slowly afforded yellow needles, apparently (by ultraviolet absorption) the 2 : 4-dinitrophenylhydrazone of the unconjugated ketone (VII). As expected, ketone (VI), with the lone methyl and the acetyl group uniplanar, does not form a 2 : 4-dinitrophenylhydrazone[4] (confirmed by the present authors), whereas the isomer (VII) to which no similar restriction applies gives the derivative with reasonable ease. An attempt to effect the isomeration (VI) ⟶ (VII) by prolonged acid treatment in the absence of 2 : 4-dinitrophenylhydrazine proved unsuccessful,



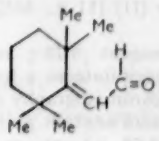
the equilibrium presumably lying predominantly towards (VI). It may be noted that substantially pure ketone (VI) results after only one distillation of the product, from the use of 98% formic acid in place of more aqueous mixtures hitherto used.

Hydrolysis of the allenic acetate (II) in the absence of dinitrophenylhydrazine might

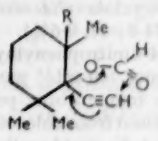
[2] Braude, *J.*, 1945, 490.
[3] Braude and Wheeler, *J.*, 1955, 321.
[4] Henbest and Woods, *J.*, 1952, 1150.

afford the aldehyde (IV), which has not yet been described. However, fairly vigorous conditions (methanolic hydrogen chloride at room temperature for three hours) yielded, not the conjugated aldehyde (IV), but the isomeric unconjugated 2 : 2 : 6-trimethyl*cyclo*hex-1-enylacetaldehyde (V) characterised by its ultraviolet and infrared absorption spectra [bands at 2700 (w) and 1715 (s) cm.$^{-1}$] and by a yellow 2 : 4-dinitrophenylhydrazone. Hydrolysis for shorter times gave different proportions of the aldehydes (IV) and (V) and unchanged acetate (II), as shown by the different intensities of the infrared bands at 1665, 1715, 1750, and 1970 cm.$^{-1}$; similar mixtures were also obtained by heating the allenic acetate (II) with aqueous acetic acid under varying conditions, thus pointing to a ready prototropic change even in weakly acid medium. In no case was the conjugated aldehyde obtained pure, for the isomers and starting material could not be separated on the scale used. However, light-absorption properties of the impure conjugated aldehyde agreed well with those of the corresponding aldehyde prepared in the tetramethyl series (see below) where a prototropic rearrangement cannot take place.

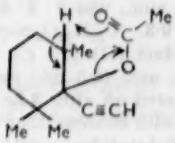
A further example of this pyrolysis was provided by the conversion of 1-ethynyl-2 : 2 : 6 : 6-tetramethyl*cyclo*hexylacetate into 2 : 2 : 6 : 6-tetramethyl*cyclo*hexylidenevinyl acetate in excellent yield (89%). Elimination of acetic acid is now impossible since no α-hydrogen atom is available. The tetramethyl allenic compound showed light absorption similar to that of the trimethyl analogue, *i.e.*, no ultraviolet maximum and strong infrared bands at 1970 and 1750 cm.$^{-1}$. It gave the red 2 : 4-dinitrophenylhydrazone of the conjugated aldehyde (VIII), and was hydrolysed quantitatively by acid to the aldehyde (VIII). A hypsochromic shift of the infrared conjugated carbonyl stretching frequency from 1665 cm.$^{-1}$ for the trimethyl to 1695 cm.$^{-1}$ for the tetramethyl compound, as well as the low-intensity ultraviolet absorption [$\lambda_{max.}$ 2480 Å; ε 5418; a mixture containing approx. 50% of trimethyl-aldehyde (IV) gave $\lambda_{max.}$ 2440 Å, ε 4931], suggested steric hindrance to the existence of a planar enone system. Inspection of models showed that even in the less sterically hindered *s-trans*-form (VIII) considerable interference occurs between a methyl group and the aldehyde-hydrogen atom. There is, however, no steric hindrance to the formation of a 2 : 4-dinitrophenylhydrazone.



(VIII)



(IX)



(X)

A plausible mechanism for the rearrangement of acetylenic acetates to allenic acetates involves a six-membered cyclic transition state (IX).[5] In the trimethyl series where R = H a rival cyclic transition state (X) competes with (IX) and results in elimination of acetic acid [6] with formation of the enyne system in (III). A necessary stereochemical condition for the formation of the cyclic form (X) is for the acetate and the 2-hydrogen atom to be located *cis* with respect to each other. It is tempting to postulate that the *cis*-isomer gives the enyne (III) while the *trans*-isomer, which cannot form (X), is converted into the allenic acetate *via* (IX). If that were so the yields of the products (II) and (III) indicate the ratio of *trans*- and *cis*-compounds present in the acetate (I). However, the acetylenic acetate (I) used as starting material was composed of sharp-melting crystals, obtained in 70% yield, and although the possibility of a mixture cannot be excluded it seems rather unlikely. From the stereochemical point of view the 6-methyl group in 2 : 2 : 6-trimethyl*cyclo*hexanone should be predominantly in the less hindered equatorial position; attack by the acetylene anion similarly will be from the less hindered side of the molecule, placing the 1-ethynyl (axial) and the 6-methyl group (equatorial) *cis* to each other. Thus the 1-hydroxyl group and the 6-hydrogen atom are also *cis* to each other,

[5] Lacey, *J.*, 1954, 827.
[6] Barton, *J.*, 1949, 2174.

and the *cis*-isomer should predominate in the product. A 70% yield of the corresponding crystalline acetate (OAc and H *cis*) would appear reasonable on this basis. Both transition states (IX) and (X) are now capable of formation and the two mechanisms are competitive.

Attempts to convert 1-ethynyl*cyclo*hexyl acetate and 1-phenylprop-2-ynyl acetate into the corresponding allenic acetates met with little success. In the former case 1-ethynyl-*cyclo*hexene was the main product, the presence of 2-hydrogen atoms unimpeded by methyl groups favouring a mechanism of type (X). 1-Phenylprop-2-ynyl acetate, on the other hand, gave a small distillate possessing the distinctive odour of cinnamaldehyde and yielding the 2 : 4-dinitrophenylhydrazone of the atter, but the bulk of the product was an intractable brown polymer.

The only previous reference to an allenic acetate is by Zakharova [7] who converted 3-chloro-3-methylbut-1-yne into a mixture of acetates by warming it with silver acetate in acetic acid at 60°. 3-Methylbuta-1 : 2-dienyl acetate was isolated in 37% yield together with smaller quantities of 1 : 1-dimethylprop-2-ynyl acetate and 1 : 2-diacetoxy-3-methylbut-2-ene. In view of the conditions used (polar medium, low temperature) in this case the allenic acetate is not likely to be produced by intramoiecular rearrangement of the acetylenic acetate but is probably formed by an S_Ni2' mechanism by the action of acetate ion on the chloroacetylene.

Experimental

Ultraviolet spectra were determined in 95% EtOH (unless otherwise specified) by using a Unicam S.P.500 spectrophotometer, and infrared spectra in CS_2 with a Perkin-Elmer Model 21 double-beam instrument. M. p.s were determined on a Kofler block. The acetylenic acetates were purified until there was no hydroxyl band in the infrared apectra.

2 : 2 : 6-*Trimethyl*cyclo*hexylidenevinyl Acetate* (II).—Pyrolysis of 1-ethynyl-2 : 2 : 6-trimethyl-*cyclo*hexyl acetate [1] (31 g.; m. p. 59—60°) with zinc oxide (6 g.) in Silicone oil (25 g.; MS 550) gave, by working up in light petroleum (b. p. 40—60°), washing with aqueous sodium hydrogen carbonate, and fractionation through a 6" column filled with Dixon rings, two main fractions; the first, b. p. up to 90°/15 mm. (7 g., 31%), rapidly becoming pink in the air, was 1-ethynyl-2 : 2 : 6-trimethyl*cyclo*hexene (III), absorption max. at 2270 Å (ε 11,000); the second, b. p. 81—83°/0·5 mm., was 2 : 2 : 6-*trimethyl*cyclo*hexylidenevinyl acetate* (II) (11 g., 35%) (Found : C, 74·7; H, 9·3. $C_{13}H_{20}O_2$ requires C, 74·9; H, 9·6%).

The product (*II*) (0·4 g.) with 2 : 4-dinitrophenylhydrazine reagent [0·75 g. of the base in sulphuric acid (2·5 ml.) and methanol (40 ml.)] gave a red precipitate in a few seconds; this was filtered off after 3 hr. at room temperature, purified by chromatography on alumina and elution with benzene, then recrystallised from chloroform–methanol solution, giving 2 : 2 : 6-*trimethyl*cyclo*hexylideneacetaldehyde* 2 : 4-*dinitrophenylhydrazone* (0·58 g.), m. p. 182—183° (Found : C, 59·2; H, 6·45; N, 16·1. $C_{17}H_{22}O_4N_4$ requires C, 59·0; H, 6·4; N, 16·1%), absorption max. (in $CHCl_3$) at 3870 Å (ε 31,300) [Henbest and Woods [4] give m. p. 214—215°, $\lambda_{max.}$ 3800 Å (ε 31,500)].

2 : 2 : 6-*Trimethyl*cyclo*hex*-1-*enylacetaldehyde* (V).—Concentrated hydrochloric acid (3) ml. was slowly added to a solution of 2 : 2 : 6-trimethyl*cyclo*hexylidenevinyl acetate (1 g.) in methanol (15 ml.) so as to keep the solution homogeneous. Heat was evolved. After 3 hr. at room temperature, the mixture was diluted with water and worked up in ether, giving on distillation the *aldehyde*, b. p. 81—83°/3 mm., absorption max. at 2960 Å (ε 36), 2 : 4-*dinitrophenylhydrazone*, yellow plates (from methanol–chloroform), m. p. 118—119° (Found : C, 58·5; H, 6·3; N, 16·2. $C_{17}H_{22}O_4N_4$ requires C, 59·0; H, 6·4; N, 16·2%), absorption max. (in $CHCl_3$) at 3590 Å (ε 22,700).

Further hydrolysis in methanolic hydrochloric acid for 5 min. and isolation with ether gave a product with $\lambda_{max.}$ 2440 Å (ε 4931) and some of the 2 : 4-dinitrophenylhydrazone identical with that of (II) above.

Isomerisation of 1-*Ethynyl*-2 : 2 : 6-*trimethyl*cyclo*hexanol*.—The alcohol (5 g.) was isomerised in 90% formic acid (cf. Henbest and Woods [4]). Isolation with ether gave a product (3·2 g.), b. p. 84—90°/20 mm., absorption max. at 2400 Å (ε 1590). No 2 : 2 : 6-trimethyl*cyclo*hexylideneacetaldehyde 2 : 4-dinitrophenylhydrazone was obtained on adding 2 : 4-dinitrophenylhydrazine reagent, even after standing overnight at 0°, from either the distillate or the residue in the flask.

[7] Zakharova, *Zhur. obshchei Khim.*, 1945, **15**, 429.

A further isomerisation of the alcohol (5 g.), carried out in 98% formic acid (20 ml.) for 1 hr., gave, on isolation with ether, 1-acetyl-2 : 2 : 6-trimethyl*cyclo*hexene (3·4 g.), b. p. 86—90°/20 mm., absorption max. at 2430 Å (ε 1290). With 2 : 4-dinitrophenylhydrazine reagent this gave, in 2 weeks at room temperature, *2-acetyl*-1 : 1 : 3-*trimethyl*cyclo*hex*-3-*ene* 2 : 4-*dinitrophenylhydrazone* as yellow needles, m. p. 152—154° (from methanol–chloroform) (Found : C, 58·9; H, 6·7; N, 16·15. $C_{17}H_{22}O_4N_4$ requires C, 59·0; H, 6·4; N, 16·1%), absorption max. (in $CHCl_3$) at 3710 Å (ε 25,000).

1-*Ethynyl*-2 : 2 : 6 : 6-*tetramethyl*cyclo*hexyl Acetate*.—1-Ethynyl-2 : 2 : 6 : 6-tetramethyl*cyclo*hexanol (prepared from 2 : 2 : 6 : 6-tetramethyl*cyclo*hexanone by sodium acetylide in liquid ammonia in 77% yield; b. p. 92°/15 mm. after one repetition of the procedure on the crude product) was acetylated *via* the Grignard compound (cf. Attenburrow *et al.*[1]) and recrystallised from ethanol, giving the *acetate*, as needles, m. p. 96° (Found : C, 75·3; H, 9·8. $C_{14}H_{22}O_2$ requires C, 75·5; H, 9·9%).

2 : 2 : 6 : 6-*Tetramethyl*cyclo*hexylidenevinyl Acetate*.—Pyrolysis of 1-ethynyl-2 : 2 : 6 : 6-tetramethyl*cyclo*hexyl acetate (4 g.) gave, after working up and fractionation, 2 : 2 : 6 : 6-*tetramethyl*cyclo*hexylidenevinyl acetate*, b. p. 132°/17 mm. (3·2 g., 89%) (Found : C, 75·6; H, 9·9. $C_{14}H_{22}O_2$ requires C, 75·5; H, 9·9%). This gave 2 : 2 : 6 : 6-*tetramethyl*cyclo*hexylideneacetaldehyde* 2 : 4-*dinitrophenylhydrazone*, m. p. 181° (after chromatography and recrystallisation from methanol–chloroform) (Found : C, 59·9; H, 6·7; N, 15·8. $C_{18}H_{24}O_4N_4$ requires C, 60·0; H, 6·7; N, 15·5%), absorption max. (in $CHCl_3$) at 3840 Å (ε 28,200).

2 : 2 : 6 : 6-*Tetramethyl*cyclo*hexylideneacetaldehyde* (X).—Hydrolysis of the foregoing acetate (1 g.) in methanol (15 ml.) with concentrated hydrochloric acid (3 ml.) gave, after distillation, the *aldehyde*, b. p. 105—106°/6 mm., absorption max. at 2480 Å (ε 5418). The 2 : 4-dinitrophenylhydrazone had m. p. 181° alone or mixed with the specimen described above.

The authors are indebted to Dr. B. A. Hems of Glaxo Laboratories for a gift of 2 : 2 : 6-trimethyl*cyclo*hexanone, Dr. G. D. Meakins of Manchester University and Mr. R. F. Branch of the Ministry of Supply for infrared spectra, and Mr E. S. Morton for microanalyses. We thank Professor E. R. H. Jones, F.R.S., for his interest in the work.

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212. *Some 2 : 6-Diamino- and 2-Amino-6-hydroxy-derivatives of 5-Aryl-4 : 5-dihydropyrimidines. A New Synthesis of 4-Alkyl-5-arylpyrimidines.*

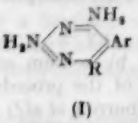
By GEORGE H. HITCHINGS, PETER B. RUSSELL, and NORMAN WHITTAKER.

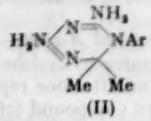
α-*cyclo*Alkylidene-α-arylacetonitriles condense with guanidine to give 2 : 6-diamino-5-aryl-4 : 5-dihydropyrimidine-4-*spirocyclo*alkanes (VII; R = NH_2). Where the aryl group is *p*-chlorophenyl it has been shown that the rate of formation of the diaminodihydropyrimidines is dependent on the size of the *cyclo*alkane ring. The mechanism of this reaction is discussed. The diaminodihydropyrimidines are readily hydrolysed by mineral acid to the corresponding 2-amino-6-hydroxy-derivatives (VII; R = OH). Analogous dihydropyrimidines (III), some of which have strong antimalarial activity, are also obtained from ββ-dialkyl-α-arylacrylonitriles. Guanidine condenses with α-arylacrylonitriles or their β-substituted derivatives, or a mixture of an aldehyde and an arylacetonitrile, to give 2-amino-5-aryl-4 : 5-dihydro-6-hydroxypyrimidines (XIV), which are dehydrogenated by sulphur to the 2-amino-5-aryl-6-hydroxypyrimidines (XV). With aqueous ammonia at 155°, 5-*p*-chlorophenyl-4-ethyl-2 : 6-dimercaptopyrimidine gave a mixture of isomeric aminomercaptopyrimidines.

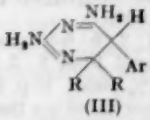
A SERIES of 2 : 4-diamino-6-alkyl-5-arylpyrimidines (I; R = alkyl) has recently shown outstanding activity against experimental malaria infections in mice and chicks.[1] Moreover, 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (Daraprim) (I; Ar = *p*-C_6H_4Cl,

[1] Falco, Goodwin, Hitchings, Rollo, and Russell, *Brit. J. Pharmacol.*, 1951, **6**, 185.

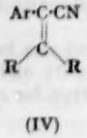
R = Et) has value in the chemotherapy of human malarias.[2] The similarity in structure of these pyrimidines to 4 : 6-diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (II; Ar = *p*-C_6H_4Cl), the antimalarial metabolite[3] of proguanil (Paludrine), prompted an investigation of a possible synthesis of some related 5-aryl-4 : 5-dihydropyrimidine derivatives (III).

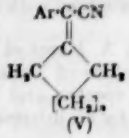

(I)


(II)


(III)

Benzophenone, *cyclo*hexanone, and *cyclo*pentanone are known to condense readily with phenylacetonitrile in alkaline solution to give αββ-triphenylacrylonitrile and α-*cyclo*alkylidene-α-phenylacetonitriles.[4] By this method acetone, diethyl ketone, benzophenone, and some cyclic ketones have now been condensed with *p*-chlorophenylacetonitrile and, in a few instances, with 3 : 4-dichlorophenylacetonitrile and *p*-methoxyphenylacetonitrile, to give the corresponding compounds (IV; R = alkyl or Ph) and (V; n = 2—5); it was not possible to prepare the *cyclo*butane (V; Ar = *p*-C_6H_4Cl; n = 1). There was no evidence to show that any isomeric *cyclo*alk-1-enylarylacetonitriles (VI) were present in the products derived from the cyclic ketones. The acrylonitrile derivatives (IV) and (V) have a light absorption in the ultraviolet characteristic of a styrene structure (see Table 2).


(IV)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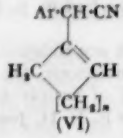
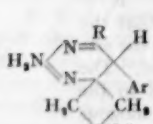
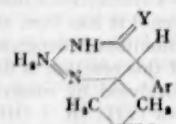
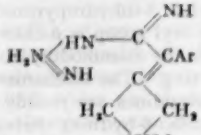
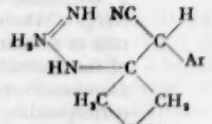

(VI)

The *cyclo*alkylidenearylacetonitriles (V) condensed with guanidine, to give crystalline basic products which are formulated as spirans (VII; R = NH_2). The presence of only an inflexion at *ca.* 245 mμ in the ultraviolet absorption of these products supports this representation rather than that of monocyclic iminoacylguanidines (IX), and structure (X) is unlikely since this type of compound should cyclise readily to the favoured structure (VII; R = NH_2). The diaminodihydropyrimidines (VII; R = NH_2) are stable to alkali but are readily and quantitatively hydrolysed by aqueous mineral acid to the 4-hydroxy-analogues (VII; R = OH). This lability to acid is not surprising since the compounds may be regarded as cyclic iminoacylguanidine derivatives, and imino-*p*-toluoylguanidine,


(VII)


(VIII)


(IX)


(X)

for example, is readily hydrolysed to *p*-toluoylguanidine.[5] Although the two series of dihydropyrimidines have been formulated as (VII; R = NH_2 or OH) they may equally exist in the imino- and keto-forms (VIII; Y = NH or O). In fact, this ready hydrolysis suggests that (VIII) (or a similar prototropic modification) may be the correct formulation.

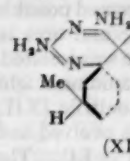
[2] Hitchings, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1952, **46**, 467; Rollo, *ibid.*, p. 485; Coatney, Myatt, Hernandez, Jefferey, and Cooper, *ibid.*, p. 496; *Amer. J. Trop. Med. Hyg.*, 1953, **2**, 777.

[3] Carrington, Crowther, Davey, Levi, and Rose, *Nature*, 1951, **168**, 1080.

[4] Stobbe and Zeitschel, *Ber.*, 1901, **34**, 1963; Birch and Kon, *J.*, 1923, **123**, 2440; Jackman, Nachod, and Archer, *J. Amer. Chem. Soc.*, 1950, **72**, 716; cf. Harding and Haworth, *J.*, 1910, **97**, 486; Jackman, Bohlen, Nachod, Tullar, and Archer, *J. Amer. Chem. Soc.*, 1949, **71**, 2301.

[5] Russell and Hitchings, *J. Amer. Chem. Soc.*, 1950, **72**, 4922.

The structures (VII) and (VIII) contain an asymmetric carbon atom at position 5 of the pyrimidine ring, but attempts to resolve a representative member (VII; Ar = *p*-C_6H_4Cl, R = NH_2, *n* = 3) failed. The tautomeric possibilities in this type of compound are, however, such that racemisation might occur. When the compound (XI) was prepared, the crystalline product recrystallised very slowly and incompletely from supersaturated methanolic solutions, suggesting that it was a mixture of stereoisomers, since the micro-analytical data agreed well with those calculated for the compound: this compound contains three asymmetric centres and four racemates are therefore possible.



(XI)

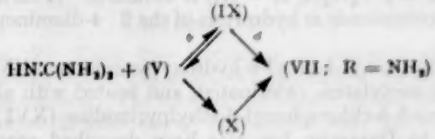
The influence of the size of the *cyclo*alkylidene ring of the nitriles (V; Ar = *p*-C_6H_4Cl, *n* = 2—5) on their rate of condensation with guanidine is quite marked. Table 1 gives the percentage conversions into the dihydropyrimidines (VII; Ar = *p*-C_6H_4Cl, R = NH_2) under standard conditions: conversion is readiest with the *cyclo*hexylidene compound.

TABLE 1. *Conversion* (*and recovery*) *of the nitriles* (V; Ar = *p*-C_6H_4Cl) *into the pyrimidines* (VII; R = NH_2).

n	2	3	4	5
2 Hr. heating: conversion (%)	50 *	68	28	7
,, recovery (%)	40	†	66	48
18 Hr. heating: conversion (%)	88 *	94	75	39

* Isolated as the sparingly soluble naphthalene-2-sulphonate. † An oil.

This reaction involves an increase in the co-ordination number of the β-carbon atom of the nitrile (V) from three to four, and it has been shown by Brown and his co-workers [6] that several reactions where this condition holds are favoured by rings of six carbon atoms, in comparison with those of five and seven. Although the comparison of reaction velocities through the yields of products obtained is admittedly open to error, the results suggest that in our condensation the rate-determining step consists of an addition reaction at the ethylenic bond. Whether this addition follows, or precedes, addition at the nitrile group is, however, not known. If reaction involved the intermediate (IX), step (*a*) would then be fast in relation to (*b*), but since large proportions of nitrile (V) were recovered after insufficient periods of reaction, step (*a*) would then have to be reversible also. A reversible reaction of this type seems not unlikely, however, by analogy with the reaction of guanidine with *p*-tolunitrile.[5]

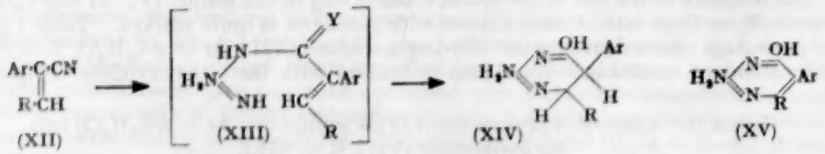


For the preparation in quantity of the diaminospiran (VII; Ar = *p*-C_6H_4Cl, R = NH_2, *n* = 3) it proved more convenient to condense *p*-chlorophenylacetonitrile with *cyclo*hexanone and guanidine directly. The 5-(3 : 4-dichlorophenyl) and 5-(2 : 4 : 5-trichlorophenyl) analogues were also obtained in good yield by this method, but direct condensation of *cyclo*pentanone or *cyclo*heptanone with *p*-chlorophenylacetonitrile and guanidine gave only small yields of the required compounds, contaminated with substantial quantities of *p*-chlorophenylacetamide.

α-*p*-Chlorophenyl-ββ-diphenylacrylonitrile (IV; Ar = *p*-C_6H_4Cl, R = Ph) was unchanged after being heated with alcoholic guanidine, but under these conditions the ββ-dialkyl-α-arylacrylonitriles (IV; Ar = *p*-C_6H_4Cl or 3 : 4-$C_6H_3Cl_2$, R = Me or Et) gave viscous oily bases which are formulated as (III) These bases formed crystalline hydrochlorides but, like the related spirans, they were hydrolysed readily and quantitatively by aqueous mineral acid to the corresponding 6-hydroxy-derivatives.

[6] Brown, Fletcher, and Johannesen, *J. Amer. Chem. Soc.*, 1951, **73**, 212.

Condensation of urea with acrylic acid and α-methylacrylic acid gives the dihydro-derivatives of uracil and thymine respectively.[7] Dihydropyrimidines have also been prepared [8] by condensation of urea with an aldehyde and a β-keto-ester. It seemed possible that *cyclo*hexanone would condense similarly with *p*-chlorophenylacetonitrile and urea in the presence of sulphuric acid, but only a mixture which contained no chlorine was isolated. Again, it was thought that a β-substituted α-arylacrylonitrile (XII) and guanidine might give a 2 : 6-diaminopyrimidine. However, when 2-*p*-chlorophenylpent-2-enonitrile (XII; Ar = *p*-C_6H_4Cl, R = Et) was heated with alcoholic guanidine, ammonia was evolved and the product was the 2-amino-6-hydroxypyrimidine (XIV; Ar = *p*-C_6H_4Cl, R = Et). The behaviour of α-*p*-chlorophenyl- (XII; Ar = *p*-C_6H_4Cl, R = H) and αβ-diphenyl-acrylo-



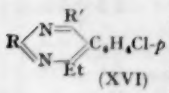
nitrile (XII; Ar = R = Ph) was analogous, the 2-amino-6-hydroxy-derivatives being obtained. This reaction probably proceeds with the intermediate formation of iminoacyl-guanidines (XIII; Y = NH), hydrolysis to acylguanidines (XIII; Y = O) preceding ring closure. To obtain the 2-amino-6-hydroxypyrimidines (XIV) in quantity, the preliminary preparation of the acrylonitrile derivatives (XII) was not essential since direct condensation of guanidine with the appropriate arylacetonitrile and aldehyde afforded satisfactory yields of the pyrimidines.

Fischer and Roeder [7] prepared uracil and thymine by brominating the corresponding dihydro-derivatives and then removing hydrogen bromide with pyridine or alkali. The dihydropyrimidines (XIV) were conveniently dehydrogenated by sulphur at 180—190°, giving the corresponding 2-amino-5-aryl-6-hydroxypyrimidines (XV) in good yield. Dehydrogenation by chloranil was less satisfactory. Four compounds of type (XV) were obtained in this manner, of which three were known. The only other method available for the preparation of 4-alkylpyrimidines of type (XV) is the reaction of α-aryl-β-keto-esters with guanidine in 20% oleum.[9] These esters do not react with guanidine base [10] but it is now found that, by heating ethyl 2-*p*-chlorophenyl-3-oxopentanoate with guanidine carbonate in alcohol, a minute yield of 2-amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxy-pyrimidine (XV; Ar = *p*-C_6H_4Cl, R = Et) is obtained. A further new procedure for the preparation of such compounds is hydrolysis of the 2 : 4-diaminopyrimidines, but the yields are only moderate.

2-Amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine (XV; Ar = *p*-C_6H_4Cl, R = Et) was successively acetylated, chlorinated, and heated with alcoholic ammonia at 160°, yielding 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (XVI; R = R′ = NH_2) (Daraprim). This route to Daraprim has also been described recently [9] by the workers of Rhône-Poulenc who began their synthesis with 2-amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine prepared from ethyl 2-*p*-chlorophenyl-3-oxopentanoate. A further method is to heat 2-amino-5-*p*-chlorophenyl-4-ethyl-6-mercaptopyrimidine (XVI; R = NH_2, R′ = SH) with alcoholic ammonia at 180°. This thiol was obtained by treating the corresponding 6-hydroxypyrimidine with phosphorus pentasulphide in tetralin at *ca.* 170°. Under similar conditions the dihydro-compound (XIV; Ar = *p*-C_6H_4Cl, R = Et) was also converted into the thiol (XVI; R = NH_2, R′ = SH) in moderate yield, dehydrogenation accompanying and, probably, preceding introduction of sulphur. When either of these 6-hydroxy-derivatives was treated with phosphorus pentasulphide at higher temperatures (190°), 5-*p*-chlorophenyl-4-ethyl-2 : 6-dimercaptopyrimidine (XVI; R = R′ = SH) alone

[7] Fischer and Roeder, *Ber.*, 1901, **34**, 3751.
[8] Biginelli, *Ber.*, 1891, **24**, 1317; Folkers and Johnson, *J. Amer. Chem. Soc.*, 1932, **54**, 3751; 1933, **55**, 1140, 2886, 3784.
[9] Jacob, B.P. 730,472.
[10] Russell and Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 3763.

resulted, and at intermediate temperatures mixtures of the 2-amino-6-mercapto- and the 2 : 6-dimercapto-pyrimidine were produced. By heating 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (XVI; R = R′ = NH_2) with phosphorus pentasulphide in tetralin at 190°, 5-*p*-chlorophenyl-4-ethyl-2 : 6-dimercaptopyrimidine (XVI; R = R′ = SH) was again obtained but in small yield. The dithiol with aqueous ammonia at 155° gave a 1 : 4 mixture of 2-amino-5-*p*-chlorophenyl-4-ethyl-6-mercaptopyrimidine (XVI; R = NH_2, R′ = SH) with the isomeric derivative (XVI; R = SH, R′ = NH_2). The formation of the 2-aminopyrimidine is surprising since 2 : 4-dimercaptopyrimidines previously examined give the 4-amino-2-mercapto-derivatives exclusively under these conditions.[11] Since the completion of our work the compound (XVI; R = SH, R′ = NH_2) has been prepared by another route.[12] The aminomercaptopyrimidines (XVI; R = NH_2, R′ = SH, and *vice versa*) with methyl iodide and alkali yielded the respective methylthio-compounds. Surprisingly, neither of these reacted with alcoholic ammonia at 160—170°, or with amines, but they were reduced by Raney nickel to 2- and 4-amino-5-*p*-chlorophenyl-6-ethylpyrimidine (XVI; R = NH_2, R′ = H and *vice versa*).



(XVI)

Our colleagues, Dr. L. G. Goodwin and Mr. I. M. Rollo, report that 2 : 6-diamino-5-(3 : 4-dichlorophenyl)-4 : 5-dihydro-4 : 4-dimethylpyrimidine is active against *Plasmodium gallinaceum* in chicks at 1 mg./kg. (inactive at 0·1mg./kg.) and against *P. berghei* in mice at 10 mg./kg. (inactive at 1 mg./kg.) and that its 5-*p*-chlorophenyl analogue is almost as active against these plasmodia [Pyrimethamine (Daraprim) (I; Ar = *p*-C_6H_4Cl, R = Et) is active against both *P. gallinaceum* and *P. berghei* at 0·1 mg./kg., but inactive at 0·01 mg./kg.]. In contrast, the 4 : 4-diethyl compounds have only a trace of activity against *P. gallinaceum* at 200 mg./kg., and the spirans (VII; R = NH_2) have no antimalarial activity. This is not surprising, for by replacing the *iso*propyl group of proguanil—in effect, the methyl groups of its metabolite (II; Ar = *p*-C_6H_4Cl)—by a larger substituent a similar decrease in antimalarial activity results.[13] It is noteworthy that these 4 : 4-dialkyl-4 : 5-dihydropyrimidines showed no activity against a strain of *P. gallinaceum* which had been made resistant to Pyrimethamine.

Our colleague, Dr. R. A. Neal, finds that the 4 : 4-dialkyl-2 : 6-diamino-5-aryl-4 : 5-dihydropyrimidines and a number of the spiran analogues (VII; R = NH_2) are active against *Entamoeba histolytica* in rats given 6 daily oral doses of 250 mg./kg. One of these compounds, 2 : 6-diamino-5-(3 : 4-dichlorophenyl)-4 : 5-dihydro-4 : 4-dimethylpyrimidine, is active at 125 mg./kg.

Experimental

Acrylonitriles (IV) *and* (V) (*Table* 2).—A mixture of equimolecular quantities of the appropriate arylacetonitrile and ketone was added to a solution of one atomic equiv. of sodium in 6—7 equivs. of anhydrous ethanol. The solution was usually heated under reflux for 30 min., cooled (crystallisation occurred in some cases), and diluted with water. Sulphuric acid was added to pH 5—6, the product extracted with ether, the extract washed with water and dried (Na_2SO_4), and the ether removed. In some instances the residual oil crystallised spontaneously and one crystallisation (method A) yielded the pure acrylonitrile; in the other cases the residual oil was distilled under reduced pressure, and the fraction containing the product was dissolved in light petroleum (b. p. 60—80°), or benzene–light petroleum, filtered from arylacetamide, and then poured through a short column of activated alumina. After removal of the solvent from the eluate, some of the residual acrylonitriles could then be crystallised (method B), but others were oils which were finally redistilled (method C).

In addition to the compounds listed in Table 2, 1-(p-*chlorophenylcyanomethylene*)-3-*methylcyclohexane* was prepared from *p*-chlorophenylacetonitrile and 3-methyl*cyclo*hexanone and was purified by method C. It was a pale yellow oil (50%) (presumably a mixture of *cis*- and *trans*-isomers), b. p. 133—134°/0·17 mm., part of which crystallised at 0° during several weeks (Found : C, 73·1; H, 6·75; Cl, 14·1. $C_{15}H_{17}NCl$ requires C, 73·3; H, 6·5; Cl, 14·45%).

[11] Russell, Elion, Falco, and Hitchings, *J. Amer. Chem. Soc.*, 1949, **71**, 2279.
[12] Baker, Schaub, Joseph, McEvoy, and Williams, *J. Org. Chem.*, 1953, **18**, 133.
[13] Curd and Rose, *J.*, 1946, 729.

TABLE 2. *ββ-Dialkyl(or diaryl)-α-arylacrylonitriles* (IV) *and* (*arylcyanomethylene*)cyclo*alkanes* (V).

Ar	R	Method of purifn.	Cryst. from	M. p. or b. p./mm.	Yield (%)	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl	$\lambda_{max.}$ (mμ) †	ε
Nitriles (IV)																
p-C_6H_4Cl	Me	C	—	162—164°/12	42	$C_{11}H_{10}NCl$	68·6	5·15	7·15	18·45	69·0	5·2	7·3	18·55	247·5	12,800
p-C_6H_4Cl	Et	C	—	162—169°/8	33	$C_{12}H_{12}NCl$	70·8	6·4	6·3	16·45	71·1	6·4	6·4	16·2	246	11,500
3 : 4-$C_6H_3Cl_2$	Me *	A	EtOH	106—107°	78	$C_{11}H_9NCl_2$	58·2	4·35	6·15	31·45	58·5	4·0	6·2	31·4	250	13,000
3 : 4-$C_6H_3Cl_2$	Et *	B	MeOH	47—49	21	$C_{12}H_{11}NCl_2$	61·7	5·15	5·5	27·95	61·5	5·1	5·5	28·0	249	11,000
p-C_6H_4Cl	Ph	A	EtOH	143—144	15	$C_{17}H_{14}NCl$	80·3	4·6	4·15	—	79·9	4·45	4·45	—	239 319	25,200 16,100
Nitriles (V)																
Ar	n															
p-C_6H_4Cl	2	A	EtOH	75—76	31	$C_{12}H_{12}NCl$	71·6	5·4	6·45	16·3	71·7	5·5	6·45	16·3	260	17,000
p-C_6H_4Cl	3	B	MeOH	43—44	37	$C_{14}H_{14}NCl$	72·65	5·9	5·95	15·4	72·6	6·05	6·05	15·35	250	15,200
p-C_6H_4Cl	4	A	EtOH	117—118	53	$C_{15}H_{16}NCl$	73·55	6·7	5·75	14·2	73·3	6·5	5·7	14·45	250	12,500
p-C_6H_4Cl	5	B	MeOH	63—64	21	$C_{16}H_{18}NCl$	73·9	6·95	5·35	—	74·0	6·95	5·4	—	250	12,000
3 : 4-$C_6H_3Cl_2$	2 *	A	EtOH	81—82	55	$C_{13}H_{11}NCl_2$	61·8	4·6	5·6	28·3	61·9	4·35	5·55	28·2	261	14,400
3 : 4-$C_6H_3Cl_2$	3	B	MeOH	64—65	45	$C_{14}H_{13}NCl_2$	63·1	5·15	5·3	26·05	63·2	4·9	5·25	26·7	250	13,500
p-MeO-C_6H_4	3	C	—	128°/0·05	15	$C_{11}H_{17}ON$	79·35	7·3	6·15	—	79·3	7·5	6·15	—	265	8,500

* Prepared by setting the mixed reactants aside for 24 hr. at room temperature. † In EtOH.

TABLE 3. 2 : 6-*Diamino*-5-*aryl*-4 : 5-*dihydropyrimidine*-4-spirocyclo*alkanes* (VII; R = NH_2) *and* 4 : 4-*dialkyl*-2 : 6-*diamino*-5-*aryl*-4 : 5-*dihydropyrimidines* (III).

Ar	n	Compd.	Cryst. from	M. p.*	Formula †	Found (%) C	H	N	N ‡	Cl	Required (%) C	H	N	N ‡	Cl
Spirans (VII; R = NH_2).															
Ph	3	Base	Aq.MeOH	135°	$C_{13}H_{20}N_4$	70·1	7·8	—	—	—	70·4	7·8	—	—	—
p-C_6H_4Cl	2	Base	Aq.MeOH	153	$C_{12}H_{15}N_4Cl,H_2O$	56·7	6·2	—	—	—	56·9	6·4	—	—	—
		$C_{10}H_7$-2-SO_3H	Aq.MeOH	246—247	$C_{24}H_{23}O_3N_4SCl$		(S, 6·4)		11·75	2·95	7·30	(S, 6·6)		11·55	2·90	7·35
p-C_6H_4Cl	3	Base	MeOH	157—159	$C_{13}H_{19}N_4Cl,CH_3·OH$	59·45	6·75	17·3	—	10·7	59·5	7·15	17·35	—	11·0
p-C_6H_4Cl	4	Base	Aq.MeOH	179—181	$C_{14}H_{21}N_4Cl,\frac{1}{2}H_2O$	61·3	7·15	17·55	—	—	61·3	7·0	17·85	—	—
p-C_6H_4Cl	5	Base	Aq.MeOH	181—182	$C_{17}H_{25}N_4Cl,\frac{1}{4}H_2O$	62·05	7·5	16·7	—	—	62·3	7·35	17·1	—	—
3 : 4-$C_6H_3Cl_2$ ...	2	HCl	H_2O	186—188	$C_{12}H_{17}N_4Cl_3,H_2O$	46·4	4·9	15·15	3·85	29·2	46·0	5·2	15·3	3·85	29·2
3 : 4-$C_6H_3Cl_2$ ...	3	Base	MeOH	166—167	$C_{13}H_{19}N_4Cl_2,CH_3·OH$	54·2	6·1	15·85	—	—	53·8	6·15	15·7	—	—
2 : 4 : 5-$C_6H_2Cl_3$	3	Base	MeOH	218—219	$C_{13}H_{17}N_4Cl_3$	49·5	4·5	15·45	3·75	29·5	50·1	4·75	15·6	3·9	29·6
p-MeO-C_6H_4 ...	3	Base	Aq.MeOH	164—165	$C_{14}H_{22}ON_4$	66·75	7·7	19·65	4·6	—	67·2	7·7	19·6	4·9	—
Ar	R														
Derivatives (III).															
p-C_6H_4Cl	Me	HCl	—	244—245	$C_{12}H_{16}N_4Cl_2$	50·4	5·75	19·1	4·6	24·4	50·2	5·6	19·5	4·9	24·75
p-C_6H_4Cl	Et	HCl	H_2O	172	$C_{14}H_{20}N_4Cl_2$	53·8	6·1	17·5	4·6	22·5	53·3	6·35	17·8	4·45	22·5
		β-$C_{10}H_7·SO_3H$	EtOH	244—245	$C_{34}H_{37}O_3N_4SCl$		(S, 6·3)		11·1	—	7·15	(S, 6·6)		11·5	—	7·3
3 : 4-$C_6H_3Cl_2$ ...	Me	HCl	H_2O	278—280	$C_{12}H_{15}N_4Cl_3$	44·65	4·95	17·65	4·25	32·55	44·8	4·65	17·4	4·35	33·15
3 : 4-$C_6H_3Cl_2$ ...	Et	HCl	H_2O	180	$C_{14}H_{19}N_4Cl_3$	48·3	5·4	15·95	3·95	29·9	48·1	5·45	16·05	4·0	30·5

* M.p.s accompanied by varying degrees of decomp. † Compounds shown as solvated were dried at room temperature; others were dried at 100° in a vacuum. ‡ These are labile N values, determined by hydrolysis with 2N-sulphuric acid in the steam-bath during 30 min., then addition of an excess of sodium hydroxide and determination of the ammonia liberated (micro-Kjeldahl).

2 : 6-*Diamino*-5-*aryl*-4 : 5-*dihydropyrimidine*-4-spirocyclo*alkanes* (VII; R = NH_2) (Table 3). —(*a*) The nitrile (V) was treated with 1·1 equivs. of 0·8N-alcoholic guanidine (prepared from guanidine hydrochloride and alcoholic sodium ethoxide), the mixture being heated under reflux for 18 hr., cooled, and diluted slowly with *ca.* 3 volumes of water, with seeding. Light petroleum (b. p. 60—80°), or a little benzene, was then added, with shaking, to dissolve any unchanged starting material and, after 3 hr., the crystalline product was collected and washed with water and benzene. The spirans (VII; R = NH_2, n = 3, 4, and 5) crystallised from methanol or aqueous methanol in a solvated form, but the analogues where n = 2 did not crystallise readily and were converted into the naphthalene-2-sulphonate or hydrochloride by adding 1 equiv. of concentrated aqueous naphthalene-2-sulphonic or hydrochloric acid to an ice-cooled solution of the base in aqueous alcohol or acetone respectively. With one exception (VII; Ar = *p*-C_6H_4Cl, R = NH_2, n = 5), all the spirans were obtained in good yield (see also Table 1). 2 : 6-*Diamino*-5-p-*chlorophenyl*-4 : 5-*dihydropyrimidine*-4-spiro-(3-*methyl*cyclo*hexane*) crystallised from methanol in colourless prisms, m. p. 161—163° (effervescence) (Found : C, 60·15; H, 7·4; N, 16·65. $C_{16}H_{21}N_4Cl,CH_3{\cdot}OH$ requires C, 60·65; H, 7·45; N, 16·65%).

(*b*) A mixture of equimolar quantities of *p*-chlorophenylacetonitrile and *cyclo*hexanone was added to 1 equiv. of 0·8N-alcoholic guanidine. The solution was heated under reflux for 3 hr., cooled, and diluted slowly with water, with seeding, giving the spiran (VII; Ar = *p*-C_6H_4Cl, R = NH_2, n = 3) (47%). The spirans (VII; Ar = 3 : 4-$C_6H_3Cl_2$ and 2 : 4 : 5-$C_6H_2Cl_3$, R = NH_2, n = 3) were obtained similarly, in yields of 52% and 45% respectively. 2 : 6-*Diamino*-5-p-*chlorophenyl*-4 : 5-*dihydropyrimidine*-4-spiro-(4-*methyl*cyclo*hexane*), prepared from *p*-chlorophenylacetonitrile, 4-methyl*cyclo*hexanone, and guanidine, crystallised from methanol in solvated colourless prisms, m. p. 166—168° (effervescence) (Found : C, 60·2; H, 7·75; N, 16·85%).

4 : 4-*Dialkyl*-2 : 6-*diamino*-5-*aryl*-4 : 5-*dihydropyrimidines* (III) (Table 3).—The nitrile (IV) was treated with 1·1 equivs. of 0·8N-alcoholic guanidine, heated under reflux for 24 hr., cooled and diluted with an equal volume of water. The alcohol was then removed under reduced pressure at *ca.* 40°, the cooled (0°) aqueous liquid was decanted from the gum, and the gum was dissolved in dried ($CaCl_2$) acetone. The acetone was then distilled, first at atmospheric pressure, and then under reduced pressure at room temperature, and the residual gum was redissolved in dry acetone. To the ice-cooled acetone solution, concentrated hydrochloric acid was added dropwise, with shaking, to pH 5—6, and after 1 hr. at 0° the crystals of the 4 : 4-dialkyl-2 : 6-diamino-5-aryl-4 : 5-dihydropyrimidine hydrochloride (80—85% yield) were collected and washed with acetone. These hydrochlorides contained both acetone and water of crystallisation and, with one exception, were finally recrystallised from water.

2-*Amino*-5-*aryl*-4 : 5-*dihydro*-6-*hydroxypyrimidine*-4-spirocyclo*alkanes* (VII; R = OH) *and their Monocyclic Analogues* (Table 4).—A solution of 2 : 6-diamino-5-(3 : 4-dichlorophenyl)-4 : 5-dihydropyrimidine-4-*spirocyclo*hexane (16·0 g.) in hot glacial acetic acid (40 ml.) and water

TABLE 4. 2-*Amino*-5-*aryl*-4 : 5-*dihydro*-6-*hydroxypyrimidine*-4-spirocyclo*alkanes* (VII; R = OH) *and* 4 : 4-*dialkyl*-2-*amino*-5-*aryl*-4 : 5-*dihydro*-6-*hydroxypyrimidines* (*B*).

Ar	n	Compd.	Cryst. from	M. p.*	Formula	Found (%) C	H	N	Required (%) C	H	N
Spirans (VII; R = OH).											
Ph...	3	Base	Aq. MeOH	307°	$C_{15}H_{19}ON_3,H_2O$	65·7	7·8	—	65·5	7·65	
X ...	2	Base	Aq. MeOH	286	$C_{14}H_{16}ON_3Cl,H_2O$	57·2	6·3	—	56·9	6·1	—
X ...	3	Base	MeOH	307	$C_{15}H_{18}ON_3Cl,MeOH$ [a]	59·25	6·75	12·8	59·4	6·8	13·0
X ...	4	Base	MeOH	301—302	$C_{16}H_{20}ON_3Cl,MeOH$ [b]	60·35	6·8	12·2	60·5	7·1	12·45
Y ...	2	HCl	Dil. HCl	225—227	$C_{14}H_{15}ON_3Cl_3$ [c, e]	48·4	4·7	11·8	48·25	4·6	12·05
Y ...	3	Base	MeOH	316—317	$C_{15}H_{17}ON_3Cl_2$	55·2	5·3	12·95	55·2	5·2	12·9
Aryl Alkyl *Derivatives* (*B*).											
X ...	Me	Base	H_2O	245—247	$C_{19}H_{14}ON_3Cl,2H_2O$ [d]	50·45	6·3	14·35	50·15	6·25	14·6
X ...	Et	Base	H_2O	246—248	$C_{14}H_{16}ON_3Cl$ [d, f]	—	—	14·7	—	—	15·05

X = *p*-C_6H_4Cl. Y = 3 : 4-$C_6H_3Cl_2$. * With decomp.

[a] Loss on drying: Found, 10·0. Reqd., 9·9%. Found: Cl, 10·95. Reqd.: Cl, 10·95%. [b] Loss on drying: Found, 9·0. Reqd., 9·5%. [c] Loss on drying: Found, 11·9. Reqd., 12·5%. Found: Cl, 12·5. Reqd.: Cl, 12·35%. [d] Dried at 100° *in vacuo* before analysis. [e] Found: Cl, 30·5. Reqd.: Cl, 30·6%. Found: Cl, 12·45. Reqd.: Cl, 12·7%.

(120 ml.) was treated with concentrated hydrochloric acid (20 ml.) and heated under reflux for 20 min. After addition of a slight excess of aqueous sodium hydroxide and cooling, the precipitated crystalline base was collected, washed with water, and then boiled with dilute aqueous sodium hydroxide (*ca.* 1 l.) to convert any remaining hydrochloride into free base. After cooling, the product was again collected, washed with water, dried [14·2 g.; m. p. 325—326° (decomp.)] and digested with hot methanol (1 l.), giving colourless prisms (15·0 g.), m. p. 316—317° (decomp.), containing *ca.* 1 mol. of methanol of crystallisation, of the hydroxy-spiran (VII; Ar = 3 : 4-$C_6H_2Cl_2$, R = OH, n = 3). The crystals lost their solvent of crystallisation during 2 days at room temperature.

The other *hydroxy-spirans* listed in Table 4 were obtained similarly, and in almost quantitative yield, from the corresponding diamines; one of them was characterised as its hydrochloride.

2-p-*Chlorophenylpent-2-enonitrile*.—This compound was obtained from *p*-chlorophenylacetonitrile and propaldehyde by the method used for the phenyl analogue.[14] The product was a mixture of oil and crystals; ethanol was added to dissolve the oil and the crystals were collected and recrystallised from ether–light petroleum, giving colourless cubes of polymeric *nitrile*, m. p. 145° [Found: C, 68·7; H, 5·6; N, 7·5. $(C_{11}H_{10}NCl)_n$ requires C, 68·9; H, 5·2; N, 7·3%]. Evaporation of the alcoholic filtrate yielded crude monomeric nitrile.

α-p-*Chlorophenylacrylonitrile* was prepared by the method used for making α-phenylacrylonitrile.[15] It was a colourless mobile liquid, b. p. 97°/0·25 mm., consisting substantially of the monomer ($\lambda_{max.}$ 262 mμ, ε 6800), but containing some dimer (Found: N, 8·6. C_9H_6NCl requires N, 8·55%). After 4 days at 0° the liquid was viscous (ε 3500, decreasing, after 10 min. at 100°, to 1600).

2-*Amino-5-aryl-4* : 5-*dihydro-6-hydroxypyrimidines* (XIV).—(*a*) Crude 2-*p*-chlorophenylpent-2-enonitrile (10·0 g.) was heated in alcoholic guanidine (5·9 g. in 100 ml.) under reflux for 10 hr., during which ammonia was evolved. The alcohol was then removed and the residual solid was washed with ether and recrystallised from ethanol, giving 2-*amino*-5-p-*chlorophenyl*-4-*ethyl*-4 : 5-*dihydro*-6-*hydroxypyrimidine* (7 g.), m. p. 275° (Found: C, 57·0; H, 5·4; N, 16·4. $C_{12}H_{14}ON_3Cl$ requires C, 57·25; H, 5·55; N, 16·7%). This base dissolved in dilute hydrochloric acid and was reprecipitated by adding aqueous alkali.

αβ-Diphenylacrylonitrile [16] (10·0 g.) was heated in alcoholic guanidine (2·9 g. in 50 ml.) under reflux overnight. The cooled solution was treated with dilute aqueous sodium hydroxide (100 ml.), and the precipitated solid was recrystallised from aqueous ethanol, forming colourless prisms (6·7 g.) of 2-*amino*-4 : 5-*dihydro*-6-*hydroxy*-4 : 5-*diphenylpyrimidine*, m. p. 285—286° (Found: C, 72·4; H, 5·3; N, 16·0. $C_{16}H_{15}ON_3$ requires C, 72·5; H, 5·65; N, 15·85%).

2-Amino-5-*p*-chlorophenyl-4 : 5-dihydro-6-hydroxypyrimidine was obtained by reaction of α-*p*-chlorophenylacrylonitrile with guanidine as a crude solid which could not be purified. Its identity was confirmed by dehydrogenation to 2-amino-5-*p*-chlorophenyl-4-hydroxypyrimidine (see below).

(*b*) *p*-Chlorophenylacetonitrile (15·0 g.) and propaldehyde (5·8 g.) were added to alcoholic guanidine (5·9 g. in 150 ml.). The resulting solution was kept at 0° for 1 hr., then warmed gradually to 30° during 2 hr., and finally heated under reflux for 3 hr. Ammonia was liberated. Water (200 ml.) was added to the cooled solution, and the liquid was decanted from the precipitated oil. The oil on being treated with ether gave crystals which recrystallised from ethanol, giving pure 2-amino-5-*p*-chlorophenyl-4-ethyl-4 : 5-dihydro-6-hydroxypyrimidine (10 g.), m. p. 273° undepressed in admixture with material obtained by method (*a*).

Equimolar quantities of phenylacetonitrile, benzaldehyde and guanidine in ethanol in this manner gave 2-amino-4 : 5-dihydro-6-hydroxy-4 : 5-diphenylpyrimidine (30%), m. p. 284°, undepressed in m. p. in admixture with material obtained by method (*a*).

m-Chlorophenylacetonitrile (30·0 g.) and propaldehyde (11·6 g.) were added to alcoholic guanidine (11·8 g. in 200 ml.), and the resulting solution was kept at room temperature for 2 hr., then heated overnight. The cooled solution was diluted with water (600 ml.), and the precipitated solid was collected, washed with ether, and recrystallised from aqueous ethanol, yielding colourless needles (17 g.), m. p. 229—230°, of 2-*amino*-5-m-*chlorophenyl*-4-*ethy*.-4 : 5-*dihydro*-6-*hydroxypyrimidine* (Found: C, 57·5; H, 5·7; N, 16·4%).

2-*Amino*-5-(3 : 4-*dichlorophenyl*)-4-*ethyl*-4 : 5-*dihydro*-6-*hydroxypyrimidine* was obtained by heating 3 : 4-dichlorophenylacetonitrile (18·6 g.), propaldehyde (5·8 g.) and alcoholic guanidine (5·9 g. in 150 ml.) under reflux for 5 hr. and isolating the product as in the previous experiment.

[14] Murray and Cloke, *J. Amer. Chem. Soc.*, 1936, **58**, 2014.
[15] Walker, U.S.P., 2,478,990.
[16] Von Walther, *J. prakt. Chem.*, 1896, **53**, 454.

The recrystallised product (9·0 g.) had m. p. 242° (Found : C, 50·5; H, 4·8; N, 14·5. $C_{12}H_{13}ON_3Cl_2$ requires C, 50·35; H, 4·55; N, 14·7%).

2-*Amino*-5-*aryl*-6-*hydroxypyrimidines* (XV).—(*a*) An intimate mixture of the 2-amino-5-aryl-4 : 5-dihydro-6-hydroxypyrimidine (XIV) with twice its weight of sulphur was heated at 180—190° for 4 hr., hydrogen sulphide being evolved. Unchanged sulphur was extracted from the cooled mixture with carbon disulphide, and the residual solid was dissolved in cold dilute aqueous sodium hydroxide. The solution was treated with charcoal, filtered, and added dropwise to hot dilute acetic acid; the product was precipitated. In this way were prepared : 2-amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine (70%), m. p. 270° [2-acetamido-analogue, m. p. 263—264° (from aqueous ethanol) (Found : C, 57·6; H, 4·9. Calc. for $C_{14}H_{14}O_2N_3Cl$: C, 57·65; H, 4·8%)]; 2-*amino*-4-*hydroxy*-5 : 6-*diphenylpyrimidine*, colourless needles (from ethanol), m. p. 319° (Found : C, 73·0; H, 5·0; N, 16·3. $C_{16}H_{13}ON_3$ requires C, 73·0; H, 4·95; N, 15·95%); 2-amino-5-*p*-chlorophenyl-4-hydroxypyrimidine, m. p. 320° (decomp.) (from ethanol) (identical with an authentic specimen prepared by another route [10]); 2-amino-5-(3 : 4-dichlorophenyl)-4-ethyl-6-hydroxypyrimidine [2-*acetamido-analogue* (42%), m. p. 261° (Found : C, 51·5; H, 4·1. $C_{14}H_{13}O_2N_3Cl_2$ requires C, 51·5; H, 4·0%)].

(*b*) 2 : 4-Diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (12·0 g.), concentrated hydrochloric acid (100 ml.), and water (10 ml.) were heated under reflux during 5 hr. The cooled solution was diluted with water (250 ml.), made alkaline with aqueous sodium hydroxide, and filtered. The filtrate was acidified with acetic acid, giving a white precipitate which was collected and dissolved in cold 2N-sodium hydroxide. The filtered solution was added dropwise to a slight excess of boiling dilute acetic acid, yielding 2-amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine as colourless needles (2·7 g.), m. p. 284°. This material was identified with that obtained by method (*a*) as shown by its ultraviolet absorption and by the properties of its acetyl derivative.

2-*Amino*-5-p-*chlorophenyl*-4-*ethyl*-6-*mercaptopyrimidine* (XVI; R = NH_2, R′ = SH).—A mixture of 2-amino-5-*p*-chlorophenyl-4-ethyl-4 : 5-dihydro-6-hydroxypyrimidine (10·0 g.), phosphorus pentasulphide (25·0 g.), and tetralin (70 ml.) was heated at 170—175°, with stirring, during 2 hr. The cooled liquid was diluted with light petroleum (b. p. 60—80°), and the precipitated solid was collected and dissolved in concentrated aqueous ammonia. The solution was treated with charcoal, filtered, and added to dilute acetic acid, precipitating the *aminomercaptopyrimidine* which crystallised from benzene in pale yellow prisms (5·1 g.), m. p. 231° (Found : C, 53·9; H, 4·7. $C_{12}H_{12}N_3SCl$ requires C, 54·2; H, 4·5%). This compound was obtained in slightly improved yield when 2-amino-5-*p*-chlorophenyl-4-ethyl-6-hydroxypyrimidine was treated with phosphorus pentasulphide under the same conditions.

5-p-*Chlorophenyl*-4-*ethyl*-2 : 6-*dimercaptopyrimidine* (XVI; R = R′ = SH).—When the reaction described above was carried out at 190°, the product was the *dimercaptopyrimidine* which crystallised from benzene in bright yellow prisms (2·7 g.), m. p. 317° (Found : C, 51·0; H, 3·9. $C_{12}H_{11}N_2S_2Cl$ requires C, 51·0; H, 3·9%). The benzene liquors, on being kept for several days, yielded a small quantity (0·2 g.) of 2-amino-5-*p*-chlorophenyl-4-ethyl-6-mercaptopyrimidine, m. p. 229—230°.

When 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (10·0 g.) was heated with phosphorus pentasulphide (25 g.) in tetralin at 190°, the dimercaptopyrimidine (0·56 g.), m. p. 312—313°, was again obtained.

Reactions with Ammonia.—(a) 2-*Amino*-5-p-*chlorophenyl*-4-*ethyl*-6-*mercaptopyrimidine*. The aminomercaptopyrimidine (2·5 g.) was heated with saturated ethanolic ammonia (50 ml.) in an autoclave at 180° during 16 hr. The solution was evaporated *in vacuo* and the residual solid was shaken with 2N-sodium hydroxide (20 ml.), collected, and purified by reprecipitation from a solution in hot dilute acetic acid with sodium hydroxide. After crystallising from ethanol, the 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (1·0 g.) had m. p. 235°, undepressed in m. p. in admixture with an authentic specimen. From the neutralised alkaline liquors a quantity (1·1 g.) of unchanged starting material separated slowly.

(b) 5-p-*Chlorophenyl*-4-*ethyl*-2 : 6-*dimercaptopyrimidine*. The dimercaptopyrimidine (1·0 g.) and concentrated aqueous ammonia (20 ml.) were heated together at 155° in an autoclave overnight. The cooled suspension of colourless crystals was filtered and the solid (0·8 g.) was recrystallised twice from 2-ethoxyethanol, yielding 4-amino-5-*p*-chlorophenyl-6-ethyl-2-mercaptopyrimidine as colourless needles which blackened at 230—240° and had m. p. 326° (decomp.) (Found : C, 53·8; H, 4·7. Calc. for $C_{12}H_{12}N_3SCl$: C, 54·2; H, 4·5%). The ultraviolet light absorption of this compound was identical with that of the condensation product [11] of thiourea with 2-*p*-chlorophenyl-3-ethoxypent-2-enonitrile. Acidification of the ammonia

liquors with acetic acid yielded yellow crystals (0·2 g.), m. p. 215°. Recrystallised from benzene, this product had m. p. 235° and was identical with 2-amino-5-*p*-chlorophenyl-4-ethyl-6-mercaptopyrimidine.

2-Amino-5-p-chlorophenyl-4-ethyl-6-methylthiopyrimidine (XVI; R = NH_2, R′ = SMe).—A solution of 2-amino-5-*p*-chlorophenyl-4-ethyl-6-mercaptopyrimidine (1·3 g.) in methanol (20 ml.) containing 2N-sodium hydroxide (5 ml.) was treated with methyl iodide (1 ml.) and kept at room temperature overnight. Water was then added and the precipitated *methylthiopyrimidine* was collected and recrystallised from methanol, forming colourless prisms (1·2 g.), m. p. 196° (Found : C, 55·5; H, 5·0. $C_{13}H_{14}N_3SCl$ requires C, 55·8; H, 5·0%).

2-Amino-5-p-chlorophenyl-4-ethylpyrimidine.—The above methylthiopyrimidine (0·45 g.), ethanol (50 ml.), Raney nickel (2·0 g.), and sodium carbonate (0·3 g.) were heated together under reflux during 4 hr. The filtered solution was evaporated and the residual solid was crystallised from ether–light petroleum, yielding white needles of the *product*, m. p. 168° (Found : C, 61·9; H, 5·3. $C_{13}H_{13}N_2Cl$ requires C, 61·7; H, 5·15%). Its *picrate*, prepared in ethanol, crystallised from ethanol containing picric acid as yellow needles, m. p. 192—193° (Found : N, 18·5. $C_{13}H_{13}N_2Cl,C_6H_3O_7N_3$ requires N, 18·2%).

4-Amino-5-p-chlorophenyl-6-ethyl-2-methylthiopyrimidine (XVI; R = SMe, R′ = NH_2) was the product of reaction of 4-amino-5-*p*-chlorophenyl-6-ethyl-2-mercaptopyrimidine (0·5 g.) with methyl iodide in the manner described for the 2-amino-6-mercapto-analogue. Recrystallised from benzene–light petroleum, the methylthiopyrimidine (0·37 g.) had m. p. 156° (Found : C, 56·1; H, 5·3. $C_{13}H_{14}N_2SCl$ requires C, 55·8; H, 5·0%). By heating this compound (1·5 g.) with Raney nickel (5·0 g.) in ethanol (30 ml.), 4-amino-5-*p*-chlorophenyl-6-ethylpyrimidine was obtained; recrystallised from ethanol, and then from ether–light petroleum, it had m. p. 145° (Baker *et al.*[12] give m. p. 141—142°).

The authors are much indebted to Messrs. P. R. W. Baker (Beckenham) and S. W. Blackman (Tuckahoe) for the analyses, to Dr. A. J. Everett for the ultraviolet absorption spectra, and to Professor H. C. Brown for a gift of *cyclo*butanone.

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213. *The Constitution and Synthesis of Fuscin.*

By D. H. R. Barton and J. B. Hendrickson.

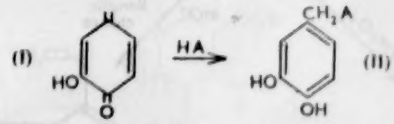
The constitution (XI) has been deduced for the mould metabolite fuscin; this formulation has been confirmed by total synthesis.

The physiologically active mould metabolite fuscin, $C_{15}H_{16}O_5$, was first isolated by Michael,[1] from the culture filtrates of *Oidiodendron fuscum* Robak. Its chemistry was the subject of an elegant and detailed investigation by Birkinshaw, Bracken, Michael, and Raistrick.[2] At the very kind invitation of Professor H. Raistrick, F.R.S., we have correlated the extensive experimental work in terms of a constitutional formula (communicated to Professor Raistrick, with fully detailed argument, in October, 1954) and have then confirmed our deductions by a total synthesis.[3]

Fuscin contains one active hydrogen atom; it forms a monomethyl ether (methylhomofuscin; see below) with diazomethane, affords a highly coloured sodium salt, and gives a positive ferric chloride test. Fuscin contains, therefore, an enolic hydroxyl group. Pyrolysis of fuscin or dihydrofuscin alone or with copper chromite and quinoline gives 1 mol. of carbon dioxide. Since fuscin is clearly not a carboxylic acid, the ready formation of carbon dioxide is best explained by the presence of a lactone grouping. Of the remaining two oxygen atoms one is inert and is revealed by the degradations (see below) as ethereal; the other must be present as a carbonyl group in order to explain the presence of the enolic hydroxyl group. The lactone-carbonyl group cannot be responsible for the enolisation, for fuscin is clearly not an enolised α- or β-keto-lactone.

[1] Michael, *Biochem. J.*, 1948, **43**, 528.
[2] Birkinshaw, Bracken, Michael, and Raistrick, *ibid.*, 1951, **48**, 67.
[3] See also Barton and Hendrickson, *Chem. and Ind.*, 1955, 682, and Birch, *ibid.*, p. 682.

We consider next the quinonoid properties of fuscin. Fuscin is easily converted into the colourless dihydrofuscin, $C_{15}H_{18}O_5$, by reduction and this behaves like a dihydric phenol, affording a diacetate and a dimethyl ether (see below). The acetylation of fuscin is analogous, addition of 1 mol. of acetic acid to the quinonoid system affording a compound (not isolated) which is further acetylated to a triacetate. Fuscin also adds readily 1 mol. of mercaptoacetic acid, of methanol, of thiourea, and of hydrogen chloride, in every case affording a colourless product. The methanol addition compound gives a diacetate on acetylation. A methylene-hydroxyquinone structure, such as (I), would be compatible with all the addition reactions [(I) ⟶ (II)] of fuscin but would not explain, without modification, the ready reversal of some of these processes (oxidation of dihydrofuscin in alkaline solution by air to furnish fuscin; elimination of hydrogen chloride from the " hydrochloride " to give back fuscin).

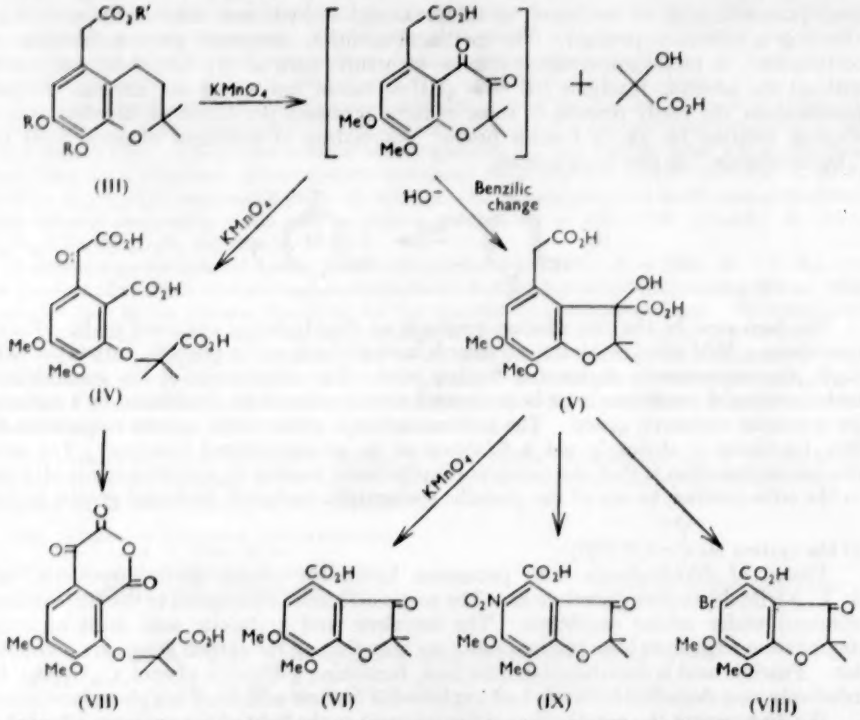


We turn now to the degradation products of dihydrofuscin obtained under alkaline conditions. Mild alkaline hydrolysis affords acetaldehyde and a phenolic carboxylic acid, $C_{13}H_{16}O_5$, conveniently designated fuscinic acid. The elimination of the acetaldehyde under such mild conditions must be a reversed aldol condensation, facilitated by a carbonyl (or potential carbonyl) group. The lactone-carbonyl group could not be responsible for this, for fuscin is obviously not a β-lactone or an αβ-unsaturated δ-lactone. The more obvious explanation is that the group in dihydrofuscin leading to acetaldehyde is attached in the *ortho*-position to one of the phenolic (potentially carbonyl) hydroxyl groups as part of the system Me·C(O–)—C(O–):C(OH)–.

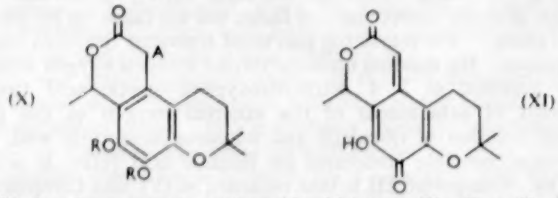
Fusion of dihydrofuscin with potassium hydroxide affords acetic, *iso*valeric, and 3 : 4 : 5-trihydroxyphenylacetic acid. The acetic acid must correspond to the acetaldehyde obtained under milder conditions. The *iso*valeric and arylacetic acid must represent degradation fragments from fuscinic acid; we note that all the carbon atoms are accounted for. Fuscinic acid is decarboxylated by heat, furnishing a dihydric phenol, $C_{12}H_{16}O_3$; the relatively easy decarboxylation is best explained if fuscinic acid itself is a phenylacetic acid.

We discuss next the constitution of fuscinic acid in the light of the evidence afforded by the products of oxidation of its dimethyl ether, $C_{15}H_{20}O_5$, with potassium permanganate. Four products were obtained: compound I, a monocarboxylic acid, $C_{13}H_{14}O_6$; compound II, a tricarboxylic acid, $C_{16}H_{16}O_{10}$; compound III, a dicarboxylic acid, $C_{15}H_{18}O_8$; and α-hydroxy*iso*butyric acid. Compound II retains all the carbon atoms and yet has three carboxyl groups. Its genesis is most simply explained by fission of the grouping ·CH_2·CH_2· in a ring. Now fuscinic acid, $C_{13}H_{16}O_5$, contains twelve hydrogen atoms less than an aliphatic compound; of these, ten are taken up by the phenolic nucleus and the carboxyl group. The remaining pair must represent the extra ring required by the oxidation experiments; the residual uncharacterised ethereal oxygen atom must be part of this ring. The isolation of 3 : 4 : 5-trihydroxyphenylacetic acid (see above) clearly indicates the point of attachment of the ethereal oxygen to the phenolic nucleus. Remembering the isolation of *iso*valeric and α-hydroxy*iso*butyric acid, we are now in a position to advance complete structures for fuscinic acid (III; R = R′ = H) and for Compound II (IV). Compound III is best regarded as (V), and Compound I as (VI). All oxidation products are formed according to the rational mechanisms indicated. In agreement with these formulations fuscinic acid dimethyl ether (III; R = Me, R′ = H) showed bands (in $CHCl_3$) at 2500—3500 and at 1708 (CO_2H), at 1590 and 1605 (benzenoid) and at 1125 cm.$^{-1}$ (ether); compound II (IV) gave bands (in Nujol) at 2600—3200 and at 1722 (CO_2H), at 1690 (CO· of CO·CO_2H), at 1580 and 1598 (benzenoid), and at 1114 and 1274 cm.$^{-1}$ (ether) [the anhydride (VII), formed from (IV) on melting, showed bands (in $CHCl_3$) at 1760 and 1840 cm.$^{-1}$ (anhydride)].

The decarboxylation and oxidation of Compound III [*i.e.*, (V)] by Br^+ and by NO_2^+ to give compounds $C_{13}H_{13}O_6Br$ (VIII) and $C_{13}H_{13}O_8N$ (IX) respectively is indicative of the α-hydroxy-acid structure ($HO\cdot\dot{C}\cdot CO_2H \longrightarrow X\text{—}O\text{—}\dot{C}\text{—}CO_2\text{—}H \longrightarrow >CO$; X = Br or NO_2) and the free aromatic position in this compound.



We are now in a position to deduce a constitution for dihydrofuscin. The group leading to acetaldehyde must (see above) be attached to the phenolic nucleus of fuscinic acid (III; R = R' = H) in the only vacant position and this then affords, on lactonisation, the structure (X; R = A = H) for dihydrofuscin. The obvious hydroxy-quinone structure for fuscin is (XI). The various addition compounds of fuscin mentioned above can be represented as (X; R = Ac, A = OAc) for the acetate derivative, as (X; R = H,

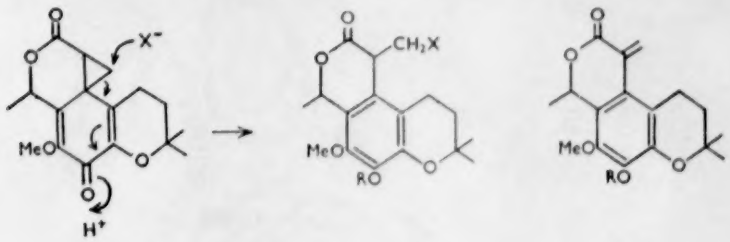


A = ·S·CH_2·CO_2H) for the mercaptoacetic acid adduct, as (X; R = H, A = OMe) and as (X; R = Ac, A = OMe) for the methanol adduct and its diacetate respectively, as (X; R = H, A = thiourea residue) for the thiourea adduct, and as (X; R = H, A = Cl) for the " hydrochloride."

In agreement with these formulations fuscin showed bands (in $CHCl_3$) at 3500 (OH), 1698 and 1668 (αβ-unsaturated δ-lactone), 1638 (αβ : α'β'-diunsaturated *cyclo*hexadienone), 1596 (C:C of this system), 1365 and 1380 (*gem*-dimethyl group) and 1112 (ether), and

dihydrofuscin showed bands (in $CHCl_3$) at 3600 (OH), 1722 (δ-lactone), 1605 and 1638 (benzenoid), 1370 and 1380 (*gem*-dimethyl), and 1118 cm.$^{-1}$ (ether).

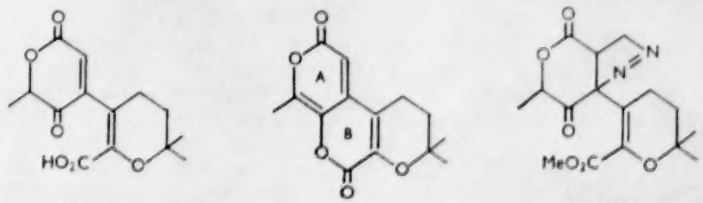
We next consider how structure (XI) explains the rest of the chemical evidence. Treatment of fuscin with diazomethane gives methylhomofuscin which may be represented as (XII). The interesting transformation products of this compound can be explained as follows. Hydrogenation gives a dihydro-derivative (XIII; R = X = H) characterised as the dimethyl ether (XIII; R = Me, X = H). Titration with alkali in the cold affords methylhomofuscin hydrate (XIII; R = H, X = OH), whilst reaction with hydrochloric acid furnishes the " hydrochloride " (XIII; R = H, X = Cl). Heating the last compound gives *iso*methylhomofuscin (XIV; R = H), also available by the more vigorous action of alkali on methylhomofuscin (XII) or by the action of iodine. Acetylation of methylhomo-



(XII) (XIII) (XIV)

fuscin hydrate (XIII; R = H, X = OH) or of the *iso*-compound (XIV; R = H) gave *iso*methylhomofuscin acetate (XIV; R = Ac). In agreement with these formulations methylhomofuscin (XII) exhibited bands (in $CHCl_3$) at 1725 (δ-lactone), 1646 (αβ : α′β′-diunsaturated *cyclo*hexadienone), 1610 (C:C of this system), 1360 and 1380 (*gem*-dimethyl), and 1113 and 1095 (ethereal). Likewise *iso*methylhomofuscin showed bands at 3550 (OH), 1720 (δ-lactone), 1605 and 1624 (benzenoid), 1118 (ether), and 895 cm.$^{-1}$ (>C:CH_2). The remarkable reactivity of the ether (XII) must be ascribed to the *cyclo*hexadienone system blocked from aromaticity by the *cyclo*propane ring. There is thus an unusually powerful driving force [see (XII)] for the rupture of the *cyclo*propane ring.

On ozonolysis fuscin breaks down smoothly to a compound, $C_{14}H_{16}O_6$, and carbon dioxide. The ozonolysis product may be formulated as (XV). When heated alone or



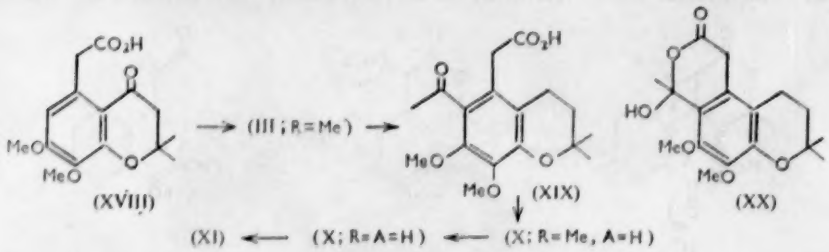
(XV) (XVI) (XVII)

with sodium acetate–acetic anhydride, or when treated with cold alkali and then acidified, this product (XV) is transformed into a yellow product, $C_{14}H_{14}O_5$ (XVI). The methylation product (diazomethane) of the compound (XV) may be represented as (XVII), or an equivalent structure. In agreement with structure (XVI), the yellow compound showed bands (in $CHCl_3$) at 1742 (CO of ring A), 1718 (CO of ring B), 1642 and 1612 (conjugated C:C), 1360 and 1380 (*gem*-dimethyl) and at 1112 cm.$^{-1}$ (ether).

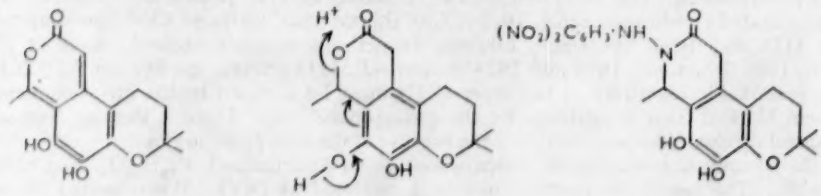
The constitution of fuscin (XI) has been placed beyond doubt by total synthesis. Treatment of methyl 3 : 4 : 5-trimethoxyphenylacetate with β-methylbut-2-enoyl chloride and aluminium chloride in ether [4] gave the keto-acid (XVIII). This showed infrared

[4] Bridge, Heyes, and Robertson, *J.*, 1937, 283.

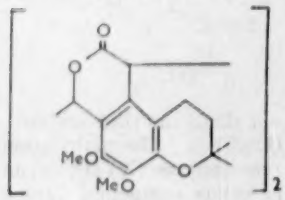
maxima (Nujol) at 1712 (CO_2H), 1672 and 1575 (·CO·C:C in a six-membered ring), 1598 and 1512 (benzenoid), 1372 and 1390 (*gem*-dimethyl), and 1300 cm.$^{-1}$ (ether) in agreement with the assigned constitution. Mild Clemmensen reduction furnished fuscinic acid dimethyl ether (III; R = Me, R′ = H). Condensation of the methyl ester (III; R = R′ = Me) with acetyl chloride and aluminium chloride as above gave the derived keto-acid (XIX), which probably existed in equilibrium with the lactol form (XX), since it showed (in $CHCl_3$) only one carbonyl band at 1754 cm.$^{-1}$. Reduction of the acid (XIX) with potassium borohydride in methanol furnished dihydrofuscin dimethyl ether (X; R = Me, A = H), demethylated under controlled Zeisel conditions [5] to dihydrofuscin (X; R = A = H), which was smoothly oxidised by air in alkaline solution to furnish fuscin (XI).



There remain for consideration those aspects of fuscin chemistry which are not at once explained by formula (XI). A possible objection is that structure (XI) has an asymmetric atom and yet fuscin and all its derivatives that we have examined are optically inactive. We believe that the asymmetric centre of fuscin must be readily racemised [see (XXI)]



and that this explains the lack of optical activity. A more serious objection is that dihydrofuscin forms a "2 : 4-dinitrophenylhydrazone." We found that the derived dimethyl ether (X; R = Me, A = H) did not react in this way and were therefore led to the view that the derivative was probably a 2 : 4-dinitrophenylhydrazide (XXII) formed as in (XXIII). The infrared spectrum of the compound (in $CHCl_3$) showed bands at 3550 (OH), 3400 (NH), 1678 (·CO·N<), 1600 and 1620 (benzenoid), and 1110 cm.$^{-1}$ (ether) in agreement with formula (XXII). The observation that dihydrofuscin (X; R = A = H) forms two dimethyl ethers when alkylated with methyl sulphate also requires comment: the major product of m. p. 98° is clearly (X; R = Me, A = H) and was obtained in the synthesis reported above; the minor product of m. p. 238—242° is probably to be formulated, in agreement with its analysis and high m. p., as (XXIV); a mechanism for the genesis of (XXIV) can be devised without difficulty provided that the presence of a small amount of fuscin is admitted. We did not encounter this high-melting product in our own methylation studies.



(XXIV)

[5] Wilds and Close, *J. Amer. Chem. Soc.*, 1947, **69**, 3079.

Experimental

Infrared spectra were kindly determined by Messrs. Glaxo Laboratories Limited. Ultraviolet absorption spectra were taken in ethanol with the Unicam S.P. 500 Spectrophotometer. Unless stated to the contrary, the light petroleum used had b. p. 60—80°.

Fuscin and its Derivatives.—Fuscin and many of its derivatives were made available by Professor H. Raistrick, F.R.S., or were prepared by known methods.[2] Improvements in two preparations were secured as detailed below.

(a) *Fuscinic acid.* Dihydrofuscin (4·38 g.) in aqueous 2N-sodium hydroxide (80 ml.) was refluxed for 13 hr. in a stream of nitrogen. Extraction with ether and separation into acidic (aqueous sodium hydrogen carbonate) and neutral fractions gave acidic material (3·18 g.). All operations were carried out under sulphur dioxide. Treatment of the acid fraction with ether gave fuscinic acid (1·52 g.). The mother-liquors were evaporated and the residue chromatographed over silica gel in 1 : 3 ether–benzene. Elution with 1 : 1 ether–benzene gave crystalline (from ether) fuscinic acid (1·37 g.). The total yield of material of m. p. 182—186° was 2·49 g.

(b) *Dihydrofuscin dimethyl ether.* Dihydrofuscin (3·1 g.) in 2N-sodium hydroxide (100 ml.) was treated under nitrogen at room temperature with good stirring with methyl sulphate (25 ml.) and 2N-sodium hydroxide (100 ml.), both reagents being added portionwise and alternately during 1—2 hr. 6N-Sodium hydroxide (40 ml.) was added and stirring continued for 3 hr. The oily product was filtered through neutralised alumina (50 g.) in 1 : 9 benzene–light petroleum. Crystallisation from light petroleum containing a little benzene gave dihydrofuscin dimethyl ether (2·0 g.), m. p. 96·5—97·5°.

Condensation of Methyl 3 : 4 : 5-Trimethoxyphenylacetate with β-Methylbut-2-enoyl Chloride.—3 : 4 : 5-Trimethoxyphenylacetic acid (6·4 g.) was converted into the methyl ester with ethereal diazomethane. The excess of diazomethane and the ether were removed *in vacuo*. The residue was taken up in dry ether (150 ml.) with addition of β-methylbut-2-enoyl chloride (3·4 ml.) and aluminium chloride (25 g.; added portionwise under reflux). The red solution was left overnight at room temperature and then poured into excess of 2N-hydrochloric acid. Extraction with ether gave the organic product. This was separated in acidic and neutral fractions with N-sodium hydroxide. Acidification and re-extraction into ether gave the desired *keto-acid* (XVIII) (750 mg.), m. p. 187—188° (from benzene–ethanol), $\lambda_{max.}$ 222 and 285 mμ (ε 19,000 and 13,700 respectively), $\lambda_{min.}$ 252 mμ (ε 1500) (Found : C, 60·6; H, 6·0. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·15%). For analysis the keto-acid was chromatographed over silica gel, elution being with chloroform; it was characterised as the 2 : 4-dinitrophenylhydrazone. Prepared in the usual way and chromatographed in chloroform solution over kieselguhr–bentonite,[6] this had m. p. 198—200° (from ethanol).

Conversion of the Keto-acid (XVIII) *into Fuscinic Acid Dimethyl Ether.*—The keto-acid (730 mg.) in aqueous 17% hydrochloric acid (18 ml.) and warm ethanol (18 ml.) was treated with amalgamated zinc (20 g.) (prepared according to Organic Reactions, Vol. I, p. 162) under reflux for 6 hr. Extraction with ether gave the total organic product. This was separated into acid and neutral fractions with aqueous sodium hydrogen carbonate. Acidification and re-extraction into ether gave fuscinic acid dimethyl ether (500 mg.), m. p. 164—168° (from ether). Purification by chromatography over silica gel and elution with 1 : 1 ether–benzene gave fuscinic acid dimethyl ether, m. p. and mixed m. p. 166—168°, $\lambda_{max.}$ 230 and 282 mμ (ε 9400 and 1200), $\lambda_{min.}$ 258 mμ (ε 550), identical with that of an authentic specimen. The identity was confirmed by comparison of infrared spectra (identical in 1% $CHCl_3$ solution).

Condensation of Methyl Fuscinate Dimethyl Ether with Acetyl Chloride.—Fuscinic acid dimethyl ether (920 mg.) was converted into the methyl ester with ethereal diazomethane in the usual way. The crude product was dissolved in dry ether (50 ml.) with addition of acetyl chloride (5 ml.) and aluminium chloride (4·0 g.; added portionwise under reflux). The dark solution was left for 3 hr. at room temperature, poured into excess of aqueous 2N-hydrochloric acid and extracted with ether. Shaking with aqueous sodium hydrogen carbonate extracted negligible amounts of acidic material from the ethereal layer. The ether was removed *in vacuo* and the residue was heated in ethanol (25 ml.) and aqueous 6N-sodium hydroxide (40 ml.) for 90 min. on the steam-bath. Separation of the product into neutral and acidic fractions gave crude acid (650 mg.). This was chromatographed on silica gel in benzene. Elution with

[6] Elvidge and Whalley, *Chem. and Ind.*, 1955, 589.

3 : 1 benzene–ether (400 ml.) gave the desired *keto-acid* (XIX) (580 mg.), m. p. 147—148° (from benzene–light petroleum), $\lambda_{max.}$ 225 and 273 mμ (ε 14,600 and 5100), $\lambda_{min.}$ 255 mμ (ε 3900) (Found: C, 63·15; H, 6·5. $C_{17}H_{22}O_6$ requires C, 63·35; H, 6·85%).

Reduction of the Keto-acid (XIX) *to Dihydrofuscin Dimethyl Ether.*—The keto-acid (XIX) (125 mg.) in methanol (20 ml.) and water was refluxed with potassium borohydride (2·2 g.; added portionwise) for 4 hr. and then left overnight at room temperature. Dilution with water, acidification with dilute sulphuric acid, extraction with ether, washing with aqueous sodium hydrogen carbonate, and removal of the ether gave a neutral product (77 mg.). Crystallisation from ether–light petroleum gave dihydrofuscin dimethyl ether, identified by m. p., mixed m. p., ultraviolet absorption [$\lambda_{max.}$ 285 mμ (ε 1500), $\lambda_{infl.}$ 230 mμ (ε 11,500), $\lambda_{min.}$ 258 mμ (ε 700); identical with that of an authentic specimen], and infrared absorption (identical with that of an authentic specimen in 1% $CHCl_3$ solution). The reduction was also effected, but less efficiently, by sodium borohydride.

Demethylation of Dihydrofuscin Dimethyl Ether.—(*a*) Dihydrofuscin dimethyl ether (560 mg.) was heated with hydriodic acid (10 ml.; *d* 1·7) and acetic acid (12 ml.) at 135—140° (reflux) in a stream of nitrogen for 5½ min. in a conventional Zeisel apparatus. A precipitate of silver iodide began to appear in the trap after 3½ min. The reaction was stopped by rapid cooling and the product, worked up in the usual way, was separated into acid (soluble in aqueous sodium hydroxide) and neutral (very small) fractions. The sodium hydroxide solution was acidified and extracted with chloroform. Removal of the chloroform *in vacuo* afforded crude dihydrofuscin (320 mg.), giving the characteristic grey-black ferric chloride reaction. Chromatography over silica gel in benzene and elution with 3 : 2 chloroform–benzene afforded crystalline dihydrofuscin (240 mg.). This was sublimed in a high vacuum to give, after one crystallisation from ether, pure dihydrofuscin, identified by m. p., mixed m. p., ultraviolet absorption [$\lambda_{max.}$ 274 mμ (ε 900), $\lambda_{min.}$ 266 mμ (ε 800), λ 210 mμ (ε 37,400); identical with that of an authentic specimen], and infrared absorption (identical with that of an authentic specimen in 1% $CHCl_3$ solution).

(*b*) Dihydrofuscin dimethyl ether (986 mg.) was heated with hydriodic acid (*d* 1·7) under the conditions specified above except that the heating was discontinued after 3½ min. The crude product, after filtration through silica gel in 1 : 1 ether–chloroform (460 mg.), was dissolved in ethanol (5 ml.) and aqueous 5% sodium hydrogen carbonate (30 ml.) with addition of aqueous 2N-sodium hydroxide (12 drops). Air was passed through this solution for 4 hr. at room temperature. Acidification of the resultant purple solution gave an orange precipitate of fuscin. Extraction with chloroform afforded crystalline fuscin (360 mg.), identified, after recrystallisation from ethanol, by crystal form (orange plates), m. p., mixed m. p., ultraviolet absorption [$\lambda_{max.}$ 355 mμ (ε 27,600), $\lambda_{min.}$ 283 mμ (ε 1000); identical with that of an authentic specimen], infrared absorption (1% solution in $CHCl_3$; identical with that of an authentic specimen), and colour reactions with ferric chloride and aqueous sodium hydrogen carbonate.

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and Imperial Chemical Industries Limited for financial assistance. One of us (J. B. H.) is indebted to the National Research Council of the U.S. for Fellowship support. We express our deep appreciation to Professor H. Raistrick, F.R.S., for his interest and encouragement. Details for the preparation of 3 : 4 : 5-trimethoxyphenylacetic acid were kindly communicated by Professor R. A. Raphael (Queen's University, Belfast). Dr. W. D. Ollis (Bristol University) gave us valuable advice at various stages in this work.

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214. *Kinetics of the Reaction between Methyl Iodide and Trimethylamine in Carbon Tetrachloride Solution.*

By R. B. Fahim and E. A. Moelwyn-Hughes.

The kinetics of the reaction between methyl iodide and trimethylamine in carbon tetrachloride have been studied experimentally in the absence of the vapour phase. Static measurements have also been made. Solutions of the halide are regular, with an interchange energy of 215 ± 7 cal./mole. Solutions of the amine are highly irregular: the activity coefficient of the solute decreases rapidly with increase in concentration in regions of kinetic interest. Tetramethylammonium iodide is insoluble in carbon tetrachloride but dissolves in the presence of either methyl iodide or trimethylamine. Crystals of the product are deposited during early stages of the reaction, and the reaction is complicated by the attainment of a heterogeneous equilibrium. In solutions containing excess of methyl iodide, the second-order velocity constant increases, and in solutions containing excess of trimethylamine it decreases as reaction proceeds. The data obtained on the kinetics of the reaction in the homogeneous phase are not inconsistent with a kinetic order of 2 and with an intrinsically low velocity coefficient.

The rate at which amines and organic halides react in solution has been the subject of numerous experimental studies since the appearance of Menschutkin's paper.[1] There have also appeared many discussions of their molecular statistics. These reactions are predominantly of the second kinetic order, though departures from a normal behaviour have been noted, particularly in solvents consisting of molecules which in the gas phase have no permanent dipole moments. Grimm, Ruf, and Wolff,[2] for example, found a drift in the second-order constants governing the reaction between ethyl iodide and trimethylamine in benzene and in *p*-dichlorobenzene. Moelwyn-Hughes and Hinshelwood[3] simultaneously and independently recorded a similar anomaly for the same reaction in carbon tetrachloride. The experimental technique employed in these and in all subsequent investigations differs little from that used by Menschutkin. The present paper records some experiments on the reaction $MeI + NMe_3 \longrightarrow NMe_4I$ in carbon tetrachloride solution carried out in the absence of the vapour phase. Its object was to extend such experimental knowledge as we now possess on the rates of chemical reactions between polar molecules in inert solvents.

Experimental

Purification of Reagents.—Methyl iodide was shaken with pellets of potassium hydroxide, washed with water, dried (Na_2SO_4), distilled from phosphoric oxide, and stored in the dark over mercury. From its vapour pressure, which was measured at 20 temperatures between 252·70° and 330·86° K, its boiling point was found to be 315·61° K, which is intermediate between the value of 315·55° given by Brown and Acree[4] and that of 315·66° given by Timmermans.[5]

The starting specimen of trimethylamine contained traces of mono- and di-methylamine, methanol, and moisture. 15-ml. samples were vaporised in a vacuum-system and cycled 3 times through bubblers containing acetic anhydride, which removed the contaminating amines, methanol, and most of the water. Two distillations at room temperatures removed most of the acetic anhydride. The next purification was by distillation at the temperature of solid carbon dioxide, passage over calcium oxide, and condensation in a trap cooled by liquid nitrogen. The liquid amine was kept over potassium for two days and finally distilled. The pure sample gave a vapour pressure[6] of 681 ± 1·0 mm. at 0°. Apiezon M grease was found to be a suitable tap

[1] Menschutkin, *Z. phys. Chem.*, 1890, **5**, 589.
[2] Grimm, Ruf, and Wolff, *ibid.*, 1931, **13**, *B*, 301.
[3] Moelwyn-Hughes and Hinshelwood, *J.*, 1932, 230.
[4] Brown and Acree, *J. Amer. Chem. Soc.*, 1916, **38**, 2145.
[5] Timmermans, "Physicochemical Constants of Pure Organic Compounds," Elsevier, Amsterdam, 1950.
[6] Swift and Hochanadel, *J. Amer. Chem. Soc.*, 1945, **67**, 880.

lubricant. Trimethylamine was estimated by titration with standard nitric acid, bromocresol-green being the indicator.

Carbon tetrachloride was washed twice with 2N-sodium hydroxide, with dilute hydrochloric acid, and finally with water. After being dried overnight over calcium oxide, and distilled from phosphoric oxide, it gave a satisfactory vapour pressure and refractive index.

Solutions of Methyl Iodide in Carbon Tetrachloride.—The equilibrium between the liquid and vapour phases of mixtures of methyl iodide and carbon tetrachloride was investigated by a standard procedure, the composition of either phase being determined refractometrically. Pressures, read on a calibrated manometer, are recorded in mm. of Hg reduced to 20°. At each temperature the relation between the total pressure, P, of the system and its compositions expressed in molar fractions, x, was examined in the light of the equation

$$P = p_1^\circ x_1 \exp(x_2^2\alpha) + p_2^\circ x_2 \exp(x_1^2\alpha) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where p_1° and p_2° are the vapour pressures of pure carbon tetrachloride and methyl iodide respectively, and

$$\alpha = \Delta U^\circ/RT \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where ΔU° is the interchange energy. Equation (1) was obeyed over all the conditions examined, so that the systems may be regarded as regular solutions in the sense applied by Hildebrand. In terms of the pressure, P, exerted by those systems which contain equimolar liquid mixtures, we have from equation (1),

$$\alpha = \Delta U^\circ/RT = 4 \ln [2P/(p_1^\circ + p_2^\circ)] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The experimental results summarised in Table 1 show that ΔU° is constant to within ± 7 cal. in the temperature range examined. Later and more precise work since completed in this

TABLE 1. *Interchange energy in the methyl iodide–carbon tetrachloride system.*

T (°K)	p_1° (mm. Hg)	p_2°	$P(x = \frac{1}{2})$	α	ΔU° (cal./mole)
283·19	55·65	219·7	152	0·396	223
303·15	139·6	492·8	345	0·348	210
313·17	210·9	699·9	495	0·334	208
323·32	309·0	966·4	694	0·339	218
333·36	443·0	1298	944	0·326	216
				Average =	215 ± 7

laboratory by Mr. R. W. Missen shows that $\Delta U^\circ = 203 \pm 2$ cal. The present data yield activity coefficients of sufficient accuracy for our needs. For systems which obey equation (1), the molar chemical potential of methyl iodide is

$$G_2 = G_2^L + RT \ln x_2 + \Delta U^\circ(1 - x_2)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where G_2^L is the molar free energy of the pure liquid. To obtain activity coefficients in the dilute regions which are of kinetic interest, we may also write

$$G_2 = G_2^\circ + RT \ln c_2 + RT \ln \gamma_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where G_2° is the molar chemical potential in an ideal solution of unit concentration (1 mole per l. of solution), and γ is the activity coefficient on this concentration basis. In dilute solutions, $x_2 = c_2 V_1^\circ/1000$, where V_1° is the molar volume of the solvent. Hence, approximately,

$$G_2^\circ = G_2^L + \Delta U^\circ + RT \ln (V_1^\circ/1000)$$

and

$$\ln \gamma_2 = -\frac{\Delta U^\circ}{RT} \cdot \frac{V_1^\circ}{500} c_2 + \frac{\Delta U^\circ}{RT} \left(\frac{V_1^\circ}{1000}\right)^2 c_2^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

At 298·16° K, V_1° is 97·10 c.c./mole. Hence

$$\log_{10} \gamma_2 = -0{\cdot}0306c + 0{\cdot}00149c^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

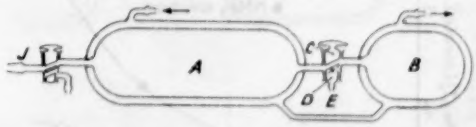
Activity coefficients of methyl iodide in dilute solutions in carbon tetrachloride derived from this equation are given in Table 2. Kinetic experiments have been confined to solutions containing initially not more than 400 mmoles of methyl iodide per l. of solution. Within this range, therefore, the solutions deviate from van't Hoff's laws by not more than 3%.

TABLE 2. *Activity coefficients of methyl iodide in carbon tetrachloride at* 298·16° K.

c_3 (mole/l.)	0	0·1	0·2	0·3	0·4
γ_3	1	0·9965	0·9862	0·9794	0·9728

Solutions of Trimethylamine in Carbon Tetrachloride.—Because of the wide difference between the vapour pressures of these two liquids, the standard method of studying the vapour–liquid equilibria is unsuitable, and was replaced by a method which depended on the direct chemical analysis of the composition of the two phases. The distribution vessel consisted of two compartments (*A* and *B*, Fig. 1) separated by a hollow tap (*C*) and surrounded by double surfaces between which thermostat water was vigorously pumped. The tap *C* was so constructed that the two compartments could be connected by means of a glass passage. When the tap is turned through 180°, access to compartment *A* was possible *via* the opening *E* and a hole *D* in the inner wall of the tap. Tap *C* is first filled with clean mercury and the clamp on opening *E* is closed. The cell is evacuated, and an appropriate amount of carbon tetrachloride is introduced, and boiled to remove traces of dissolved gases. The cell is joined to a vacuum-system through a yard of coiled copper tubing of 1·5 mm. bore, and is clamped horizontally in a cradle which can be violently rocked. Trimethylamine is cautiously admitted from a gas

FIG. 1. *Vapour–liquid distribution cell.*



burette, and the pressure of the equilibrated system is finally measured against a mercury manometer. The distribution cell is allowed to remain vertical until all the liquid has drained from compartment *A*. By careful manipulation of the taps *J* and *E* it is possible to flood both compartments separately with a known excess of aqueous nitric acid. The amount of amine in either compartment is then calculated after back titration with alkali. The partial pressure of the amine was calculated in mm. of Hg by using Berthelot's equation

$$p = \frac{\nu RT}{V}\left\{1 + \frac{9}{128}\frac{T_c}{T}\frac{p}{p_c}\left[1 - 6\left(\frac{T_c}{T}\right)^2\right]\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where ν is the number of moles of amine in V c.c. of the vapour, $R = 63{,}380$ in these units, $T_c = 433{\cdot}3°$ K, and $p_c = 40{\cdot}24$ atm.[7]

At 273·41° K experiments were made on mixtures of all compositions, but at 298·18° K and 317·86° K only with solutions containing not more than 0·5 mole-fraction of amine. The interchange energy calculated according to equation (3) was found to be neither zero nor constant. Solutions of trimethylamine in carbon tetrachloride are, therefore, neither ideal nor regular. Somewhat similar behaviour has been reported for the methanol–carbon tetrachloride

TABLE 3. *Activity coefficients of trimethylamine in carbon tetrachloride solution at* 298·16° K.

x_3	0	0·01	0·02	0·03	0·04	0·06	0·08	0·10	0·20	0·30	1·00
p_3 (mm.)	0	18	33	46	58	83	109	137	290	486	1663
γ_3	(1·70)	1·08	0·99	0·92	0·87	0·83	0·82	0·82	0·87	0·97	1·00

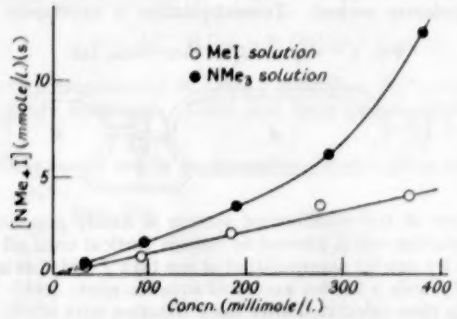
system by Scatchard and Ticknor,[8] who found it necessary to use five constants to represent the excess free energy of the solution over that of an ideal solution. Our results are not sufficiently accurate to justify such a detailed analysis, and we shall content ourselves with recording interpolated values of the activity coefficients reckoned on a mole-fraction basis (Table 3). It

[7] Day and Felsing, *J. Amer. Chem. Soc.*, 1950, **72**, 1698.
[8] Scatchard and Ticknor, *ibid.*, 1952, **74**, 3724.

will be observed that, with increasing concentration, the activity coefficient of the amine decreases rapidly until it reaches a minimum value at a molar fraction of about 0·09. The extrapolated value of γ_s at zero concentration, obtained from a logarithmic plot, is a conservative estimate. Experimental values exceeding 2 were obtained for some of the very dilute solutions. Most of our kinetic experiments were done with solutions of trimethylamine containing not more than 0·1 mole per l., corresponding to molar fractions not exceeding 0·01. During the course of the reaction, therefore, the activity coefficient of the amine rises continuously.

Solutions of Tetramethylammonium Iodide in Carbon Tetrachloride.—Repeated agitation of the finely ground salt with the pure solvent in sealed tubes at 25° showed that the salt was insoluble within the accuracy of the analytical estimation, which was 0·2 mmole per l. Solubility measurements with the pure salt and the pure solvent were then for a time discontinued. Chemical analysis of the products of the reaction between methyl iodide and trimethylamine in carbon tetrachloride solution, however, revealed the undoubted presence of inorganic iodide. It was therefore concluded that the salt, though insoluble in the pure solvent, was soluble in solutions of the products of its own decomposition. Separate experiments with solutions of either methyl iodide or trimethylamine in carbon tetrachloride proved this to be true. The results at 298·16° K are shown graphically in Fig. 2. It is impossible from these data to extrapolate a value for the solubility of the salt in the pure solvent, though it may safely be

FIG. 2.



assessed as not more than 1×10^{-4} mole/l. Vernon and Sheard [9] have measured the solubility of tetramethylammonium iodide in mixtures of ethylene dichloride and benzene. Using an empirical relation between the solubility of the salt and the dielectric constant of the mixed solvent, they estimated its solubility in pure benzene as $6{\cdot}92 \times 10^{-6}$ mole/l. As the dielectric constants of benzene and carbon tetrachloride at this temperature are very similar (2·253 and 2·219), our conclusion seems to be indirectly confirmed. The analyses of reaction products given in Table 4 indicate an approximate value of 0·022 l./mole for the term

TABLE 4. *Compositions of final solutions (mmoles/l.) at* 298·16° K.

$a = [CH_3I]_0$	$b = [NMe_3]_0$	$a - x_\infty$	$b - x_\infty$	s
97·2	37·7	59·6	0·5	0·7
105·6	106·0	4·3	4·8	0·4
174·5	37·7	137·6	0·3	1·0

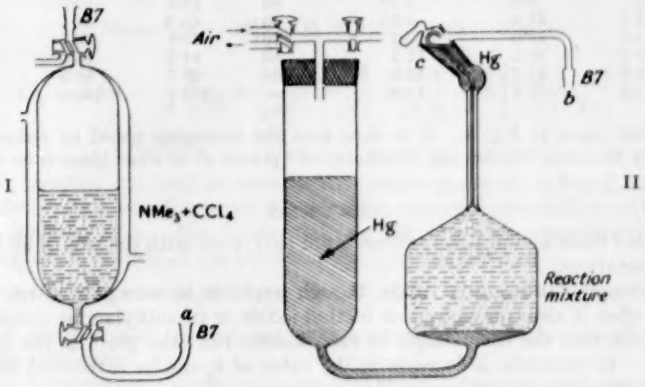
$s/(a - x_\infty)(b - x_\infty)$, where s is the concentration of salt in solution, and $a - x_\infty$ and $b - x_\infty$ are the final concentrations of methyl iodide and trimethylamine respectively in the homogeneous phase. Clearly, if we start with a solution containing equimolar proportions of the reactants at concentrations of 0·1M, chemical reaction proceeds about 96% of the way. Lower values of $s/(a - x_\infty)(b - x_\infty)$ were obtained in more dilute solutions, but the internal consistency of the analyses was less satisfactory than in Table 4.

Kinetic Procedure.—Solutions of methyl iodide were made in a conical flask connected by a ground-glass join to a tap and thence to a B7 cone; the solute was introduced from a weight pipette into the pure solvent under its own vapour pressure and at the run temperature.

[9] Vernon and Sheard, *J. Amer. Chem. Soc.*, **1948**, **70**, 2035.

Solutions of trimethylamine were prepared in vessel I (Fig. 3) by leading in the vapour at a regulated pressure from a gas-burette as in the distribution experiments. The solutions were mixed through the B7 joints and were drawn into vessel II (Fig. 3) which was included in the thermostat. At suitable time intervals 5 ml. of the mixture were expressed through tap *C* into a known excess of ice-cold aqueous nitric acid. Samples drawn from the early stages of reaction were analysed for free base by titration with hydriodic acid, and for iodide ion by titration with

FIG. 3.



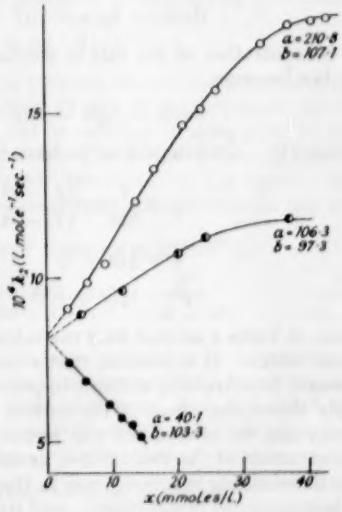


FIG. 4. *Second-order velocity coefficients at 298·23° K.*

potassium iodate. After crystals had appeared in the reaction vessels, samples were expressed through a plug of glass-wool, and only the base was estimated. The total amount of organic and inorganic iodide in initial and final samples was estimated after digestion for 10 hr. at 100° with excess of sodium methoxide in methanol solution.

Kinetic Results.—Experiments were carried out in duplicate and, unless the two agreed, in triplicate. The numerous runs at 298·23° K showed that the second-order velocity coefficients calculated from the equations

$$\frac{dx}{dt} = k_2(a - x)(b - x); \quad k_2 = \frac{1}{t(a - b)} \ln \frac{b(a - x)}{a(b - x)} \quad . \quad . \quad . \quad . \quad (9)$$

varied during the run. With methyl iodide in excess, k_2 increased with time; with trimethylamine in excess, k_2 decreased with time. The results of a typical run are shown in Table 5, and

TABLE 5. *Second-order velocity coefficients at* 298·23° K. $a = 210{\cdot}8 \pm 0{\cdot}8$; $b = 107 \pm 1{\cdot}7$.

t (min.)	x (mmoles/l.)	Change (%)	$k_2 \times 10^4$ (l. mole^{-1} sec.$^{-1}$)	t (min.)	x (mmoles/l.)	Change (%)	$k_2 \times 10^4$ (l. mole^{-1} sec.$^{-1}$)
0	0	0	—	35	47·1	44·0	15·0
5	5·8	5·4	9·10	40	52·5	49·0	15·6
10	12·2	11·4	9·88	55	65·9	61·5	17·0
15	18·2	17·0	10·3	70	75·1	70·1	17·6
20	26·9	25·1	12·3	85	81·3	75·9	17·7
25	34·1	31·8	13·3	100	86·7	80·5	17·8
30	41·6	38·6	14·6	∞	107·1	100·0	—

the general behaviour in Fig. 4. It is clear that the anomalies noted by Grimm, Ruf, and Wolff [2] and by Moelwyn-Hughes and Hinshelwood [3] persist even when there is no vapour phase present.

DISCUSSION

To interpret these kinetic observations is not easy, even with the help of all the ancillary static determinations.

That tetramethylammonium iodide, though insoluble in pure carbon tetrachloride, is soluble in it when it also contains either methyl iodide or trimethylamine is consistent with the observation that the early stages of each kinetic run take place in the homogeneous liquid phase. In principle, a decrease in the value of k_2 can be attributed to the reverse reaction, and equation (9) can be modified as follows:

$$dx/dt = k_2(a - x)(b - x) - k_1x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

where x is the concentration of the salt in solution. After the appearance of crystalline salt, the kinetic law becomes

$$dx/dt = k_2(a - x)(b - x) - k_1s \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where s is its solubility. On integrating we have:

$$k_2 = \frac{1}{2\beta t} \ln \left\{ \frac{1 - [x/(\alpha + \beta)]}{1 - [x/(\alpha - \beta)]} \right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

where $$\alpha = \tfrac{1}{2}(a + b) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

and $$\beta^2 = [\tfrac{1}{2}(a + b)]^2 - ab + (k_1/k_2)s \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

On using the data of Table 4 we find that the calculated effect of the reverse reaction is less than the observed effect. It is possible that s varies with the course of reaction. This is a point which would be extremely difficult to prove or to disprove experimentally. Fig. 2, of course, merely shows the effect of the solutes separately on the solubility of the salt. Two explanations can be offered for the increase in k_2 shown by solutions containing equimolar concentrations of the two solutes, or methyl iodide in excess of methylamine:

(1) The rate-determining reaction, even in the presence of the salt, may be assumed to proceed in the homogeneous liquid phase; and its rate may be assumed to be governed by the activities of the two reactants. Then, as shown in Tables 2 and 3, though the activity coefficient of the halide remains sensibly constant, that of the amine increases as its concentration diminishes. Velocity coefficients calculated by means of the incremental equation

$$k_2 = \frac{1}{(a - x)\gamma_2(b - x)\gamma_3} \cdot \frac{dx}{dt} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

were, on the whole, less variable than those calculated by means of equation (9). For example, the run shown in the centre of Fig. 4 gives, in terms of activities, an initial and fairly constant value of $k_2 \times 10^4 = 8{\cdot}14$, which ultimately falls to 6·85.

(2) It can be assumed that, after the appearance of crystals, the homogeneous reaction is accompanied by a heterogeneous reaction at the surface of the crystals and involving the adsorption of either solute or of both.

On the whole the second explanation is preferred because it does not rely on the illogical assumption, so often made in chemical kinetics, that γ_3 as measured for a single solute in solution is identical with its value in the presence of a second solute. If the catalytic effect were proportional to the extent of reaction, we would have, in terms of concentrations, the rate equation

$$dx/dt = k_2(a - x)(b - x) + k_3(a - x)(b - x)x \quad . \quad . \quad . \quad . \quad (16)$$

or

$$(k_2 + k_3b)t = \frac{1}{(a - b)} \ln\left[\frac{b(a - x)}{a(b - x)}\right] + \frac{1}{(a + c)} \ln\left[\frac{a(c + x)}{c(a - x)}\right] \quad . \quad . \quad (17)$$

where $$c = k_2/k_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

Equation (16), however, can only account for the positive gradients in Fig. 4, and it is clear that the catalytic effect, which is proportional to the area of the crystalline surface, cannot be a linear function of x. The differential rate law based on equations (11) and (16) describes the general features of the somewhat complicated kinetics:

$$dx/dt = k_2(a - x)\gamma_2(b - x)\gamma_3 - k_1s + k_3(a - x)\gamma_2(b - x)\gamma_3f(x) \quad . \quad . \quad (19)$$

An apparently second-order reaction can thus emerge owing to the cancellation of the second and the third term.

Influence of Temperature.—From measurements made at temperatures above and below 298·23° K, estimates can be made of the constants A and E_A of the integrated form of Arrhenius's equation

$$k_2 = A \exp(-E_A/RT) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (20)$$

Because of the relatively early deposition of crystals, these constants can only be evaluated for the heterogeneous reaction. They show (Table 6) an apparent decrease with the extent of reaction, of a magnitude which can be ascribed to adsorption of either solute on the crystal surface. In view of the complexity of the reaction, no simple interpretation of these constants can be given. If they are in fact constant, the rate of reaction between methyl iodide and trimethylamine at 100° C must be about 500 times as fast as that between

TABLE 6. *Arrhenius constants at* 298·16° K.

x (mmoles/l.)	10	20	30
E_A (cal./mole)	9760	8740	8280
A (l. mole^{-1} sec.$^{-1}$)	$1{\cdot}33 \times 10^4$	$2{\cdot}68 \times 10^3$	$1{\cdot}39 \times 10^3$

the corresponding ethyl compounds in the same solvent. It is possible, however, as Tommila and Kauranen [10] have pointed out, that they are both functions of temperature. When their observations at 325·7° K and those of Grimm, Ruf, and Wolff at 368·2° K are combined and given equal weight, the apparent energy of activation of the reaction between methyl iodide and trimethylamine in benzene solution becomes

$$E_A = (18{,}250 \pm 3250) - (9{\cdot}35 \pm 4{\cdot}75)RT$$

Menschutkin's reaction thus appears to resemble numerous other reactions in solution. To gain more precise information on the kinetics of these reactions in the homogeneous liquid phase, a new technique is required and is now being developed.

One of us (R. B. F.) is indebted to the Ministry of Education of the Egyptian Government for a fellowship, and both of us are indebted to Mr. R. H. Bathgate for assistance with some of the experimental work.

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215. *Complexes of Nickel and Cobalt with Certain Chelate Compounds.*

By S. E. Livingstone.

Four-covalent neutral complexes of bivalent nickel and cobalt with seven chelate compounds have been prepared and the magnetic moments of the crystalline products determined.

The complexes can be divided into classes: (*a*) those with moments corresponding to "ionic" or tetrahedral bonding (sp^3), and (*b*) those corresponding to "covalent" or square bonding (dsp^2). The former contain oxygen as one of the ligand atoms of the chelate group, and the latter have sulphur, together with nitrogen, sulphur, or arsenic linked to the metal atom.

In this investigation neutral complexes of bivalent nickel and cobalt with several chelate compounds have been prepared, and their stereochemistry inferred from the magnetic moments.

The quadradentate compound, 1 : 2-di-(*o*-carboxyphenylthio)ethane,

$$HO_2C{\cdot}C_6H_4{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}C_6H_4{\cdot}CO_2H$$

gave insoluble crystalline complexes with both nickel and cobalt. *o*-Methylthiobenzoic acid appears not to co-ordinate with these metals, probably because the entropy of formation is greater with the quadridentate ligand; this has been suggested as one of the main reasons for the relatively greater stabilities of complexes containing polydentate ligands (Burkin, *Quart. Rev.*, 1951, **5**, 1).

Bis-3-dimethylarsinopropane-1-thiolnickel is remarkable in that the amorphous brown product recrystallizes from alcohol as well-formed green prisms, which are very soluble in chloroform, acetone, alcohol, and nitrobenzene, forming deep brown solutions. Moreover, the compound is diamagnetic, whereas four-covalent Ni^{II} complexes, when diamagnetic, are usually red, brown, or yellow, and when paramagnetic are green or blue (Nyholm, *Chem. Rev.*, 1953, **53**, 263). The values for the molecular weight, determined cryoscopically in nitrobenzene (438, 422), correspond to that expected for the formula $Ni(C_5H_{12}SAs)_2$, *viz.*, 417.

The nickel complex of 3-ethylthiopropane-1-thiol and the cobalt complex of 3-dimethylarsinopropane-1-thiol were isolated as brown oils, the latter contaminated with excess of thiol. These oils were readily soluble in chloroform, but did not crystallize. The chelate compound, *o*-carboxyphenyldimethylarsine, $AsMe_2{\cdot}C_6H_4{\cdot}CO_2H$, which forms a well-defined crystalline complex with palladium (Livingstone and Plowman, *J. Proc. Roy. Soc. New South Wales*, 1950, **84**, 188), does not appear to co-ordinate with nickel and cobalt.

The nickel complex of *o*-aminophenol was isolated as the dihydrate (the grey crystals are stable at 120°, but in 45 min. at 145° lose the water to leave a brownish-black powder). The complex is paramagnetic in both forms (3·2 B.M.). The magnetic moment of the cobalt complex is 4·3 B.M. Mellor and Craig (*ibid.*, 1940, **74**, 475, 493) reported the nickel complex as diamagnetic and the cobalt complex with a moment of 2·5 B.M.; these values must be regarded as unreliable.

The predicted magnetic moments (μ) for bivalent nickel and cobalt, calculated from the spin-only formula, *i.e.*, $\mu = n(n + 2)$ Bohr magnetons, where n is the number of unpaired electrons, are listed in Table 1.

Table 1. *Predicted magnetic moments for bivalent nickel and cobalt.*

	No. of unpaired electrons	μ (B.M.)		No. of unpaired electrons	μ (B.M.)
Planar Ni^{II} (dsp^2)	0	0	Planar Co^{II} (dsp^2)	1	1·73
Tetrahedral Ni^{II} (sp^3)	2	2·83	Tetrahedral Co^{II} (sp^3)	3	3·87

The complexes prepared in this investigation and the magnetic data are listed in Tables 2 and 3. It was suggested by Mellor (*Chem. Rev.*, 1943, **33**, 317; *J. Proc. Roy. Soc. New South Wales*, 1945, **79**, 141) that if an element can form square complexes it will do so unless (i) it is octahedrally co-ordinated, (ii) steric effects distort the bond angles, or

(iii) the attached atom is sufficiently electronegative to favour ionic or tetrahedral bonding. When due allowance is made for the orbital contribution to the magnetic moment, which is usually high for bivalent cobalt, an examination of Tables 2 and 3 shows that where a very electronegative atom (*i.e.*, oxygen) is attached to the metal atom, the complex has a moment corresponding to a tetrahedral configuration. On the other hand, when less electronegative atoms are bonded (*i.e.*, sulphur and nitrogen, sulphur and arsenic), a

TABLE 2. *Magnetic susceptibilities of nickel complexes.*

	Colour	$10^6\chi$	$10^6\chi_m$	$10^6\chi_m$ (corr. for diamagnetism)	μ (B.M.)
1 : 2-Di-(*o*-carboxyphenylthio)ethane ...	Pale green	9·75	4151	4452	3·22
Anthranilic acid	Pale blue	12·40	4110	4327	3·20
o-Aminophenol	Grey	13·52	4208	445·4	3·22
o-Aminobenzenethiol	Greyish-yellow	−0·47	−144	—	0
o-Methylthiobenzenethiol	Orange	−0·25	−93	—	0
3-Dimethylarsinopropane-1-thiol	Green	−0·34	−144	—	0
3-Ethylthiopropane-1-thiol	Brown oil	−0·57	−186	—	0

TABLE 3. *Magnetic susceptibilities of cobalt complexes.*

	Colour	$10^6\chi$	$10^6\chi_m$	$10^6\chi_m$ (corr. for diamagnetism)	μ (B.M.)
1 : 2-Di-(*o*-carboxyphenylthio)ethane	Pink	27·61	10,800	11,050	5·09
Anthranilic acid	Pink	32·40	10,720	10,940	5·05
o-Aminophenol	Pink	26·28	7700	7907	4·03
o-Aminobenzenethiol	Dark blue	8·65	2660	2871	2·6
3-Ethylthiopropane-1-thiol	Dark green	6·94	2382	2566	2·44

square complex results. Nyholm (*Chem. Rev.*, 1953, **53**, 263) suggested that double bonding between the ligand atom and the metal atom is also an important factor favouring the square configuration. Craig, Maccoll, Nyholm, Orgel, and Sutton (*J.*, 1954, 332) state that two strong π-bonds can be formed at right angles, using 3*d* electron pairs of a transition metal atom and vacant *p* or *d* orbitals on the ligand atom. It is interesting that ligands containing atoms or groups capable of forming double bonds with the metal atom, *e.g.*, S, As, CN, do form square planar complexes with bivalent nickel and cobalt.

EXPERIMENTAL

**1 : 2-*Di*-(*o*-*carboxyphenylthio*)*ethanenickel*(II) *Dihydrate*—1 : 2-Di-(*o*-carboxyphenylthio)ethane (1 g.) was treated with one equiv. of 0·5M-sodium hydroxide and the small amount of undissolved material removed by filtration. To the hot filtrate was added a solution of nickel acetate tetrahydrate (0·5 g.) in water (20 ml.). After some minutes at the b. p., pale green crystals were precipitated. On cooling, the *nickel complex* was filtered off, washed with a small amount of hot water, then acetone, and dried over phosphoric oxide *in vacuo*. It (0·40 g.) was practically insoluble in hot water and organic solvents (Found : C, 45·4; H, 3·6; Ni, 13·4. $C_{16}H_{12}O_4S_2Ni,2H_2O$ requires C, 45·0; H, 3·8; Ni, 13·7%).

Bisanthranilatonickel(II).—Anthranilic acid (3 g.) was dissolved in boiling water (100 ml.), and an aqueous solution (20 ml.) of nickel nitrate hexahydrate (3 g.) added. After 30 sec. a crystalline precipitate began to be formed. The mixture was kept at the b. p. for 10 min. and then filtered. The pale blue crystals (12·5 g.) were washed with hot water, then acetone. The addition of sodium acetate to the filtrate precipitated more of the *compound* (Found : C, 51·0; H, 3·7; N, 8·7. $C_{14}H_{12}O_4N_2Ni$ requires C, 50·8; H, 3·7; N, 8·5%).

Bis-o-aminophenolnickel(II) *Dihydrate*.—This compound was prepared by a method similar to that used by Hieber and Schnackig (*Z. anorg. Chem.*, 1936, **226**, 209) (Found : C, 45·9; H, 5·1; N, 9·1; Ni, 18·9. Calc. for $C_{12}H_{12}O_2N_2Ni,2H_2O$: C, 46·3; H, 5·2; N, 9·0; Ni, 18·9%).

Bis-o-aminobenzenethiolnickel(II).—This compound has been described by Hieber and Bruck (*ibid.*, 1952, **269**, 13). The yellowish-grey complex was precipitated by the addition of *o*-aminobenzenethiol to an aqueous solution of nickel nitrate (Found : C, 46·9; H, 4·1; N, 9·1; Ni, 19·4. Calc. for $C_{12}H_{12}N_2S_2Ni$: C, 46·9; H, 3·9; N, 9·1; Ni, 19·1%).

Bis-o-methylthiobenzenethiolnickel(II).—*o*-Methylthiobenzenethiol (0·5 g.) was treated with one equiv. of 0·5M-sodium hydroxide, and an aqueous solution of nickel acetate (0·3 g.) added. A yellowish-brown microcrystalline precipitate (0·53 g.) was produced, which recrystallized from 70% acetone (50 ml.) as orange cubes (0·37 g.). The *nickel complex* is readily soluble in

acetone, chloroform, and nitrobenzene producing brown solutions; it had m. p. 171° (with decomp.) (Found: C, 45·3; H, 3·6; Ni, 16·3. $C_{14}H_{14}S_4Ni$ requires C, 45·5; H, 3·8; Ni, 15·9%). Conductivity at 20°: Λ_{500} in acetone, 0·01 mho; Λ_{500} in nitrobenzene, 0.

Bis-3-dimethylarsinopropane-1-thiolnickel(II).—3-Dimethylarsinopropane-1-thiol (1·0 g.) was treated with one equiv. of 0·5M-sodium hydroxide, and an aqueous solution of nickel acetate (0·38 g.) added. An amorphous brown precipitate slowly became green and crystalline. It was recrystallized from a few millilitres of alcohol, yielding green prisms (0·35 g.), m. p. 85—86°. The *compound* is readily soluble in chloroform, acetone, alcohol, and nitrobenzene to deep brown solutions (Found: C, 28·6; H, 5·7; Ni, 14·0%; *M*, cryoscopically in nitrobenzene, 438 in 0·44% and 422 in 0·30% solution. $C_{10}H_{24}S_2As_2Ni$ requires C, 28·8; H, 5·8; Ni, 14·1%; *M*, 417). The molecular conductivity at 25° of a 10^{-3}M-solution of the compound in nitrobenzene was 0·1 mho.

Reaction of 3-Ethylthiopropane-1-thiol with Ni(II).—A suspension of the thiol (1·37 g.) in water (30 ml.) containing sodium hydroxide (0·25 g.) was treated with an aqueous solution of nickel nitrate hexahydrate (1·5 g.). There was an immediate formation of a reddish-brown oil which was extracted by chloroform (50 ml.). The extract was dried (Na_2SO_4) and evaporated, leaving a viscous dark reddish-brown oil, which was diamagnetic with $\chi_g = -0{\cdot}57 \times 10^{-6}$.

1 : 2-*Di*-(*o-carboxyphenylthio*)*ethanecobalt*(II).—1 : 2-Di-(*o*-carboxyphenylthio)ethane (0·8 g.) was treated with one equiv. of 0·5M-sodium hydroxide, and the solution was filtered. The filtrate was poured into a warm solution of cobaltous acetate tetrahydrate (0·6 g.) in water (30 ml.), producing a purplish-pink amorphous precipitate, which was converted into pink prisms when the mixture was boiled for some time. The *product* (0·45 g.) was washed with boiling water, then acetone, and dried (Found: C, 48·6; H, 3·1; Co, 15·0. $C_{14}H_{12}O_4S_2Co$ requires C, 49·1; H, 3·1; Co, 15·1%).

Bisanthranilatocobalt(II).—This compound was prepared from cobalt acetate and anthranilic acid in 50% alcoholic solution (Found: C, 49·9; H, 3·7; N, 8·4; Co, 17·6. Calc. for $C_{14}H_{12}O_4N_2Co$: C, 50·8; H, 3·7; N, 8·5; Co, 17·8%).

Bis-o-aminophenolcobalt(II) *Monohydrate*.—This compound was prepared from cobalt acetate and *o*-aminophenol in aqueous-alcoholic solution (Found: C, 48·5; H, 4·9; N, 9·4. Calc. for $C_{12}H_{12}O_3N_2Co,H_2O$: C, 49·1; H, 4·8; N, 9·5%).

Bis-o-aminobenzenethiolcobalt(II).—*o*-Aminobenzenethiol (2·0 g.), in alcohol (10 ml.), was added to cobaltous acetate tetrahydrate (2·0 g.) in 50% aqueous alcohol (50 ml.) at 50°. The immediate amorphous brown precipitate was filtered off and boiled with acetone (250 ml.) for 2 hr., whereupon it became dark blue and crystalline. The *compound* was again filtered off, washed with acetone, in which it is very sparingly soluble, and dried at 110° (yield, 2·0 g.). It slowly darkens in air owing to oxidation (Found: C, 46·7; H, 3·8; N, 9·2. $C_{12}H_{12}N_2S_2Co$ requires C, 46·9; H, 3·9; N, 9·1%).

Reaction of 3-Dimethylarsinopropane-1-thiol with Co(II).—3-Dimethylarsinopropane-1-thiol (1·52 g.) in alcohol (10 ml.) was added to cobalt acetate tetrahydrate (1·0 g.) in 50% alcohol (40 ml.). A brown oil, containing the cobalt complex dissolved in excess of the thiol, was produced. The oil is soluble in chloroform to a yellowish-brown solution. The complex could not be obtained free from the thiol.

Bis-(3-ethylthiopropane-1-thiol)cobalt(II).—Cobalt acetate tetrahydrate (1·4 g.), in warm 50% alcohol (40 ml.), was treated with the thiol (1·5 g.) in alcohol (10 ml.). An amorphous pinkish-purple product was precipitated, which crystallized when the mixture was warmed. The *complex* was filtered off, washed with boiling water, and boiled with acetone (50 ml.), then filtered off again and dried (yield, 0·9 g.). The dark green iridescent crystals had a reddish-purple "streak" and were only very sparingly soluble in acetone to a reddish-purple solution. They do not melt below 250° (Found: C, 37·1; H, 6·9. $C_{10}H_{22}S_4Co$ requires C, 36·5; H, 6·8%).

Magnetic Susceptibility Measurements.—The Gouy method was employed, with a balance similar to that described by Baddar, Hilal, and Sugden (*J.*, 1949, 132). The measurements were made on the compounds in powder form at room temperature (289—294° K) (except when the compound was an oil; in this instance the measurement was made on the crude oil).

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216. *Polyazanaphthalenes. Part III.* Some Derivatives of 1 : 3 : 5- and 1 : 3 : 8-Triazanaphthalene.*

By V. Oakes, R. Pascoe, and H. N. Rydon.

A number of derivatives of 1 : 3 : 5- and 1 : 3 : 8-triazanaphthalene have been prepared from the 2 : 4-dihydroxy-compounds, the structures of which are discussed. The chlorine atoms in the 2 : 4-dichloro-compounds differ markedly in their reactivity towards bases, the 4-chlorine being the more reactive in both series. Catalytic hydrogenation of 2 : 4-dichloro-1 : 3 : 5-triazanaphthalene yields 1 : 3 : 5-triazanaphthalene, which proved too unstable to be isolated as the free base; by contrast, hydrogenation of 2 : 4-dichloro-1 : 3 : 8-triazanaphthalene yields the 5 : 6 : 7 : 8-tetrahydro-compound.

Periodate oxidation of 2-aminonicotinic hydrazide yields the corresponding aldehyde but similar oxidation of 3-aminopicolinic hydrazide yields only the amide.

This paper is concerned with an exploratory study of the chemistry of the 1 : 3 : 5- and 1 : 3 : 8-triazanaphthalenes about which there was, until very recently, little published information. Only four derivatives of 1 : 3 : 5-triazanaphthalene, *viz.*, the 4-hydroxy-, 2 : 4-dihydroxy-, 4-hydroxy-2-mercapto-, and 2-amino-4-hydroxy-compounds, have been recorded.[1,2] Before 1955, published information on 1 : 3 : 8-triazanaphthalene was also very meagre, being restricted to the 4-hydroxy-, 2 : 4-dihydroxy-, and 4-hydroxy-2-methyl compounds and certain of their derivatives.[3,4] Since the completion of our work,[5] however, Robins and Hitchings [6] have published an extensive investigation of the 1 : 3 : 8-triazanaphthalenes which, in many respects, duplicates and supplements our findings.

The most convenient starting material for the preparation of 1 : 3 : 5-triazanaphthalene derivatives is 3-aminopicolinic acid, which we prepared from quinolinimide by a modification of Sucharda's method;[7] substitution of sodium hypobromite for the hypochlorite in this preparation markedly increases the yield of 3-aminopicolinic acid at the expense of that of the unwanted by-product, 2-aminonicotinic acid. Contrary to our experience with 2-aminonicotinic hydrazide (see p. 1048), treatment of 3-aminopicolinic hydrazide with periodate afforded, not the expected aldehyde, but only 3-aminopicolinamide; amides have been prepared from hydrazides by treatment with nitrous acid [8] and with Raney nickel,[9] but these are hardly good analogies for this curious reaction.

The starting point for the major part of our work in this series was 2 : 4-dihydroxy-1 : 3 : 5-triazanaphthalene [2] (I), which is most easily prepared by fusing 3-aminopicolinic acid with urea. Considerable difficulty was experienced in replacing the two hydroxyl groups by chlorine. Reaction with phosphorus oxychloride alone gave a grey solid, containing chlorine, nitrogen, and phosphorus, from which none of the required dichloro-compound (II) could be isolated. Somewhat better results were obtained by working in the presence of dimethylaniline [10] but the yields obtained by this procedure were variable, as also were those obtained in the presence of diethylaniline. Reproducible yields were finally obtained by carrying out the reaction with phosphorus oxychloride in the presence

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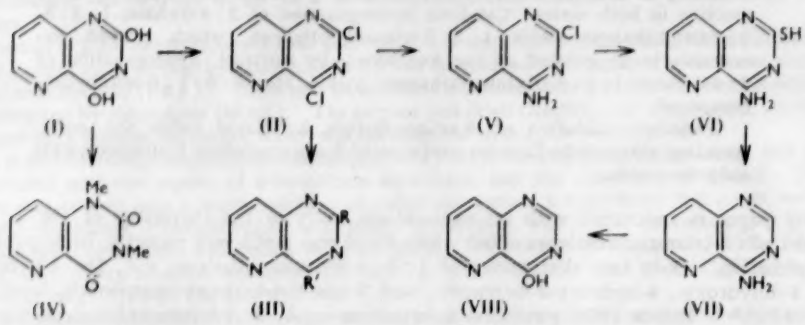
[4] McLean and Spring, *J.*, 1949, 2582.
[5] Pascoe, Thesis, London, 1952; Oakes, Thesis, Manchester, 1955.
[6] Robins and Hitchings, *J. Amer. Chem. Soc.*, 1955, **77**, 2256.
[7] Sucharda, *Ber.*, 1925, **58**, 1728.
[8] Stoll and Hofmann, *Helv. Chim. Acta*, 1943, **26**, 922; Olsen and Enkemeyer, *Chem. Ber.*, 1948, **81**, 359.
[9] Ainsworth, *J. Amer. Chem. Soc.*, 1954, **76**, 5774.
[10] Cf. Kenner, Lythgoe, Todd, and Topham, *J.*, 1943, 574.

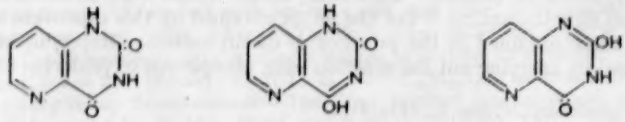
of triethylamine;[11] no evidence was obtained of the formation as by-products of the diethylamino-derivatives encountered by the American workers, although 2-chloro-4-(*N*-ethylanilino)-1 : 3 : 5-triazanaphthalene (III; R = Cl, R′ = NEtPh) was obtained on one occasion from the reaction in presence of diethylaniline.

Hydrogenolysis of the dichloro-compound (II) over Adams catalyst, with or without added magnesium oxide, proceeding smoothly, yielding 1 : 3 : 5-triazanaphthalene (III; R = R′ = H), isolated as its picrate, m. p. 191°. The free base, a low-melting waxy solid, was very unstable, decomposition and oxidation or polymerisation to red or brown insoluble materials attending all attempts at purification by crystallisation or distillation.



The chlorine atoms in (II) are very reactive, exposure to moist air being sufficient to bring about hydrolysis to the dihydroxy-compound (I), and they can be replaced by a variety of other groups; owing to its ready hydrolysis, all reactions with the dichloro-compound (II) must be carried out in anhydrous media. Reaction with thiourea, followed by treatment of the resulting bisthiuronium salt with hot water, afforded the dithiol (III; R = R′ = SH), while reaction with sodium ethyl sulphide yielded the diethylthio-compound (III; R = R′ = SEt); both of these compounds, on desulphurisation with Raney nickel, afforded the parent base (III; R = R′ = H), isolated as its picrate.

Treatment of the dichloro-compound (II) with sodium methoxide and ethoxide afforded the 2 : 4-dimethoxy- (III; R = R′ = OMe) and 2 : 4-diethoxy-compound (III; R = R′ = OEt); the former is not identical with the isomeric dimethyl derivative, obtained by treating the dihydroxy-compound (I) with dimethyl sulphate and alkali, which must therefore be the *N*-methyl derivative (IV) (cf. the similar *N*-methylation of 2 : 4 : 7-trihydroxypteridine [12]). Light-absorption curves for the dihydroxy-compound (I) and the two dimethyl derivatives are shown in Fig. 1; the similarity of the curve for the dihydroxy-compound to that for the *O*-methyl derivative (III; R = R′ = OMe), rather than to that for the *N*-methyl derivative (IV), suggests that its structure is indeed (I), rather than the



alternative diketo-structure (IX), although the monoketo-structures (X) and (XI) cannot be excluded. This conclusion is in interesting contrast to the conclusions reached, on similar evidence, concerning the structures of 2-, 4-, and 2 : 4-hydroxylated pyrimidines.[13]

[11] Cf. Robins and Christensen, *J. Amer. Chem. Soc.*, 1952, **24**, 3624.
[12] Tschesche and Korte, *Chem. Ber.*, 1951, **84**, 801.
[13] (*a*) Marshall and Walker, *J.*, 1951, 1004; (*b*) Boarland and McOmie, *J.*, 1952, 3716; (*c*) Brown and Short, *J.*, 1953, 331; (*d*) Brown, Hoerger, and Mason, *J.*, 1955, 211.

Treatment of the dichloro-compound (II) with ammonia in boiling phenol [14] yielded the diamino-compound (III; R = R′ = NH_2), whereas treatment with ammonia in cold dioxan gave an amino-chloro-compound; the chlorine in the latter compound was remarkably resistant to hydrolysis, the compound surviving boiling with water for several hours but being completely hydrolysed to the dihydroxy-compound (I) with hot 2N-sodium hydroxide. This amino-chloro-compound was shown to be 4-amino-2-chloro-1 : 3 : 5-triazanaphthalene (V) by conversion into the 4-amino-2-mercapto-compound (VI), also

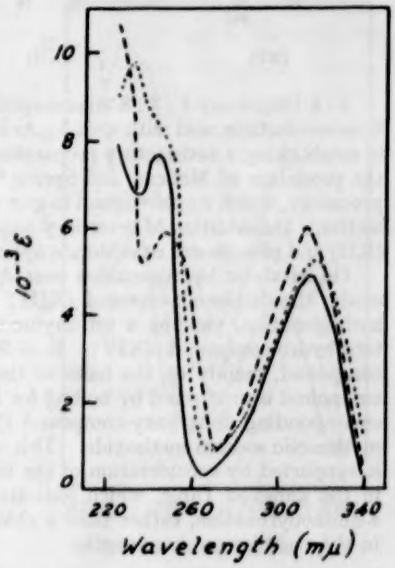


FIG. 1.

Light absorption, in ethanol, of 2 : 4-*dihydroxy*-1 : 3 : 5-*triazanaphthalene* (I) (——), 2 : 4-*dimethoxy*-1 : 3 : 5-*triazanaphthalene* (III; R = R′ = OMe) (– – – –), *and* 1 : 2 : 3 : 4-*tetrahydro*-1 : 3-*dimethyl*-2 : 4-*dioxo*-1 : 3 : 5-*triazanaphthalene* (IV) (. . . .).

obtained by the action of ammonia on the dithiol (III; R = R′ = SH), followed by Raney nickel desulphurisation to the 4-amino-compound (VII), which was finally converted, by acid hydrolysis, into the 4-hydroxy-compound (VIII), identical with material prepared from 3-aminopicolinic acid and formamide.[1] Similar preferential reactivity of the 4-chlorine atom in (II) has also been observed towards diethylamine and 3-diethylaminopropylamine.

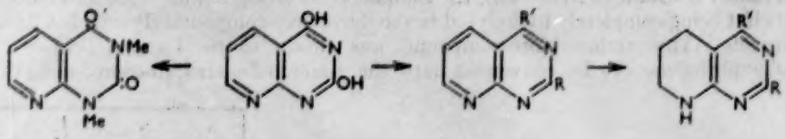
The great reactivity of the 4-, as compared with the 2-, chlorine atom in (II) is in marked contrast to the approximately equal reactivities of the two chlorine atoms in 2 : 4-dichloropyrimidines [15] and recalls the enhanced reactivity of the 4-chlorine in 2 : 4-dichloro-5-nitropyrimidines [16] and in 2 : 4-dichloroquinazoline.[17] Curd, Landquist, and Rose [17] explain this enhanced reactivity on the basis of inductive electron-withdrawal from the 4-position by the neighbouring nitro-group or benzene ring and a similar explanation probably applies also in our case. The presence of the pyridine nitrogen does not seem to be of great importance since a similar enhanced reactivity of the 4-chlorine is also observed in 2 : 4-dichloro-1 : 3 : 8-triazanaphthalene (see below and ref. 6).

Distillation of the dihydroxy-compound (I) with zinc dust afforded a crystalline product, $C_6H_5N_3$, m. p. 152°; this appears to be 1 : 3 : 4-triazaindene.[18]

The starting material for our work in the 1 : 3 : 8-triazanaphthalene series was 2-aminonicotinic acid, which was prepared from quinolinic monoamide by the method of Phillips.[19]

[14] Cf. Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 753.
[15] Gabriel, *Ber.*, 1905, **38**, 1689; Hilbert and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 1153.
[16] Gabriel and Colman, *Ber.*, 1901, **34**, 1234; Isay, *Ber.*, 1906, **39**, 252.
[17] Cf. Curd, Landquist, and Rose, *J.*, 1947, 775.
[18] Petrow and Saper, *J.*, 1948, 1389.
[19] Phillips, *Annalen*, 1895, **288**, 253.

Periodate oxidation [20] of 2-aminonicotinic hydrazide or, better, of its *iso*propylidene derivative (acetone 2-aminonicotinoylhydrazone), yielded 2-aminonicotinaldehyde which, however, gave no isolable 1 : 3 : 8-triazanaphthalene with formamide.



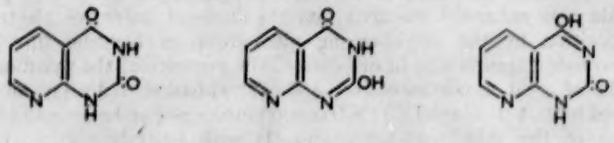
(XV) (XII) (XIII) (XIV)

2 : 4-Dihydroxy-1 : 3 : 8-triazanaphthalene (XII) was conveniently prepared by fusing 2-aminonicotinic acid with urea.[6] As in the 1 : 3 : 5-series, we experienced some difficulty in establishing a satisfactory preparation of the dichloro-compound (XIII; R = R′ = Cl), the procedure of McLean and Spring [4] being often unsuccessful in our hands. A simple procedure, which we have found to give reproducible yields, is described in the Experimental section; the addition of a tertiary base in the reaction between the dihydroxy-compound (XII) and phosphorus oxychloride appears to be without advantage.

On catalytic hydrogenation over Adams catalyst, with or without added magnesium oxide, the dichloro-compound (XIII; R = R′ = Cl) underwent, not hydrogenolysis, but hydrogenation, yielding a tetrahydro-derivative. This is formulated as the 5 : 6 : 7 : 8-tetrahydro-compound (XIV; R = R′ = Cl), rather than the 1 : 2 : 3 : 4-tetrahydro-compound, mainly on the basis of the relative unreactivity of the chlorine atoms; the compound is unaffected by boiling for 10 minutes with N-sodium hydroxide and yields the corresponding dimethoxy-compound (XIV; R = R′ = OMe) on prolonged heating with methanolic sodium methoxide. This view of the structure of the hydrogenation product is supported by consideration of the light-absorption data (solutions in ethanol) collected in the annexed Table, which indicate that the hydrogenation product is a chlorinated 4-aminopyrimidine, rather than a chlorinated 2-aminopyridine which would be expected to absorb at longer wavelengths.

Compound	$\lambda_{max.}$ (mμ)	$\log_{10}\varepsilon$
2 : 4-Dichloro-1 : 3 : 8-triazanaphthalene (XIII; R = R′ = Cl)	252, 307	3·95, 4·03
Hydrogenation product (XIV; R = R′ = Cl)	252, 290	4·17, 3·89
2-Aminopyridine [21]	290	3·58
4-Aminopyrimidine [13b]	236, 272	4·30, 3·71
4-Amino-2 : 6-dichloropyrimidine [22]	248, 284	4·30, 3·71

McLean and Spring [4] showed that methylation of the dihydroxy-compound (XII) with dimethyl sulphate afforded the *N*-methyl derivative (XV), whereas the action of sodium methoxide on the dichloro-compound (XIII; R = R′ = Cl) yielded the isomeric *O*-methyl compound (XIII; R = R′ = OMe). Light-absorption curves for ethanolic solutions of



(XVI) (XVII) (XVIII)

these two compounds and the dihydroxy-compound (XII) are shown in Fig. 2. As in the 1 : 3 : 5-series the comparison supports the dihydroxy-structure (XII) rather than the diketo-structure (XVI), although it does not completely exclude the mono-keto-structures (XVII) and (XVIII).

[20] Cf. Wingfield, Harlan, and Hanmer, *J. Amer. Chem. Soc.*, 1952, **74**, 5796.
[21] Spiers and Wibaut, *Rec. Trav. chim.*, 1937, **56**, 573.
[22] Calc. from the data for 4-aminopyrimidine by the method of Boarland and McOmie, ref. 13*b*.

The dichloro-compound (XIII; R = R′ = Cl) is less susceptible to hydrolysis than its isomeride in the 1 : 3 : 5-triazanaphthalene series but nevertheless undergoes replacement reactions readily. Reactions with sodium ethyl sulphide afforded the 2 : 4-diethylthio-compound (XIII; R = R′ = SEt); an attempt to obtain 1 : 3 : 8-triazanaphthalene by Raney nickel desulphurisation of this compound was unsuccessful. Reaction of the dichloro-compound (XIII; R = R′ = Cl) with ammonia [6] afforded the 2 : 4-diamino-

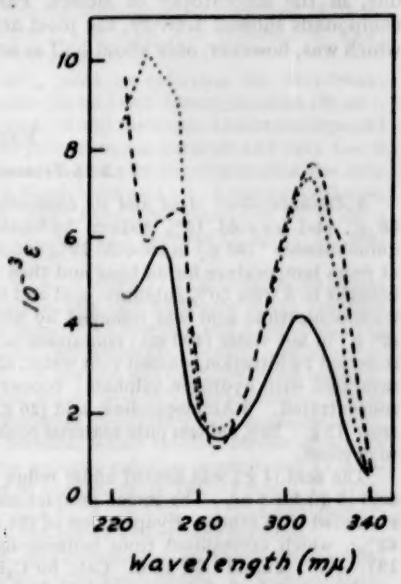


FIG. 2.

Light absorption, in ethanol, of 2 : 4-*dihydroxy*-1 : 3 : 8-*triazanaphthalene* (XII) (——), 2 : 4-*dimethoxy*-1 : 3 : 8-*triazanaphthalene* (XIII; R = R′ = OMe) (– – – –), and 1 : 2 : 3 : 4-*tetrahydro*-1 : 3-*dimethyl*-2 : 4-*dioxo*-1 : 3 : 8-*triazanaphthalene* (XV) (. . . .).

compound (XIII; R = R′ = NH_2) or the 4-amino-2-chloro-compound (XIII; R = Cl; R′ = NH_2) according to the severity of the reaction conditions. Alkaline hydrolysis converts all these compounds into the parent dihydroxy-compound (XII).

Like Robins and Hitchings,[6] we, too, prepared 4-hydroxy-1 : 3 : 8-triazanaphthalene (XIII; R = H, R′ = OH) both by heating 2-aminonicotinic acid with formamide (cf. Klisiecki and Sucharda [3]) and by Raney nickel desulphurisation of the 4-hydroxy-2-mercapto-compound (XIII; R = SH; R′ = OH), obtained from 2-aminonicotinic acid and thiourea.

As in the pteridines,[23] so also in the 1 : 3 : 5- and 1 : 3 : 8-triazanaphthalenes, the presence of groups capable of hydrogen bonding markedly raises the melting point and lowers the solubility. This is well brought out in the annexed Table of melting points.

Substituents 2-	4-	1 : 3 : 5-Triazanaphthalene	1 : 3 : 8-Triazanaphthalene *	Substituents 2-	4-	1 : 3 : 5-Triazanaphthalene	1 : 3 : 8-Triazanaphthalene *
OH	OH	>380°	361° (365°)	Cl	NH_2	265°	>360° (>310°)
SH	OH	>360	360 (355—356)	H	NH_2	224	(299—301)
H	OH	345	256 (258)	Cl	Cl	173	160 (158—159)
SH	SH	340	(>360)	OMe	OMe	138	144
NH_2	NH_2	318	342 (356)	SEt	SEt	56	76
NH·NH_2	NH·NH_2	266	(348—350)				

* Melting points in parentheses are those recorded by Robins and Hitchings.[6]

A curious feature is the apparent tendency for 1 : 3 : 5-triazanaphthalenes with a hydroxyl-group in the 4-position to melt considerably higher than, and those with an

[23] Albert, Brown, and Cheeseman, *J.*, 1951, 474; 1952, 4219.

amino-group in this position considerably lower than, the corresponding 1 : 3 : 8-triazanaphthalenes; this may, perhaps, be connected with a tendency for 4-hydroxyl, but not 4-amino-, groups to form hydrogen bonds with a ring-nitrogen atom at position 5.

In view of the useful antituberculosis activity of *iso*nicotinic hydrazide [24] the action *in vitro* of 2-aminonicotinic, 3-aminopicolinic, and 3-amino*iso*nicotinic hydrazides on *Mycobacterium tuberculosis* was investigated by Dr. M. W. Fisher, to whom our thanks are due, in the laboratories of Messrs. Parke, Davis, and Company in Detroit; all three compounds showed activity, the most active of them being 3-amino*iso*nicotinic hydrazide which was, however, only about half as active as *iso*nicotinic hydrazide itself.

Experimental

1 : 3 : 5-*Triazanaphthalene derivatives.*

3-Aminopicolinic Acid and its Derivatives.—Aqueous sodium hypobromite (from bromine, 56 g., and ice-cold 15% sodium hydroxide solution, 350 ml.) was added to a solution of quinolinimide [7] (50 g.) in ice-cold 10% sodium hydroxide solution (1 l.). The mixture was kept at room temperature for an hour and then at 85° for a further hour; after cooling, the pH was brought to 5 with 50% sulphuric acid and the mixture kept at 2° for 48 hr. A small amount of 2-aminonicotinic acid was removed by filtration and the filtrate treated with copper acetate (20 g.) in hot water (400 ml.) containing acetic acid (10 ml.). The precipitated copper salt was collected by filtration, washed with water, and resuspended in water (400 ml.), and the suspension saturated with hydrogen sulphide; copper sulphide was removed by filtration and the filtrate concentrated. 3-Aminopicolinic acid (26 g.; 56%), m. p. 210°, separated on cooling; a further crop (13 g.; 28%) of less pure material could be obtained from the mother-liquor by evaporation to dryness.

The acid (4 g.) was heated under reflux on the steam-bath with ethanol (8 g.) and sulphuric acid (8 g.) for 4 hr. The cooled product was poured on ice, basified with aqueous ammonia and extracted with ether. Evaporation of the dried extract afforded ethyl 3-aminopicolinate (2 g.; 42%), which crystallised from benzene–light petroleum in needles, m. p. 132° (lit.,[25] m. p. 131—133°) (Found : N, 16·6. Calc. for $C_8H_{10}O_2N_2$: N, 16·9%). This ester (1·6 g.) was heated on the steam-bath for an hour with hydrazine hydrate (1 g.); crystallisation of the product from ethanol afforded *3-aminopicolinic hydrazide* (0·9 g., 61%) in needles, m. p. 103° (Found : C, 46·7; H, 5·0. $C_6H_8ON_4$ requires C, 47·4; H, 5·3%), which, on refluxing with acetone, followed by concentration, yielded *acetone 3-aminopicolinoylhydrazone* (71%) in plates, m. p. 172° (Found : N, 29·0. $C_9H_{12}ON_4$ requires N, 29·2%).

The hydrazide (700 mg.), suspended in water (10 ml.) and ammonia solution (*d* 0·880; 2 ml.), was slowly added to an ice-cold solution of sodium metaperiodate (1·1 g.) in water (15 ml.) and aqueous ammonia (10 ml.). After 35 minutes' shaking, barium acetate (1·2 g.), in water (5 ml.), was added and the precipitated barium salts were removed by filtration. The filtrate was brought to pH 7, saturated with sodium chloride, and extracted with chloroform. Evaporation of the extract and recrystallisation of the residue from benzene afforded 3-aminopicolinamide (350 mg., 55%) in plates, m. p. 184° (lit.,[26] m. p. 175—177°) (Found : C, 53·0; H, 5·2. Calc. for $C_6H_7ON_3$: C, 52·6; H, 5·1%); the m. p. was not depressed on admixture with a specimen of the amide prepared by passing ammonia into a mixture of ethyl 3-aminopicolinate and ammonia solution, and the identity was further confirmed by mixed m. p. of the derived picrate, needles, m. p. 214°.

2 : 4-Dihydroxy-1 : 3 : 5-triazanaphthalene (I).—A finely powdered intimate mixture of 3-aminopicolinic acid (13 g.) and urea (7 g.) was heated slowly to 190—200° and then kept at this temperature for 30 min. The cooled product was dissolved in 2N-sodium hydroxide (200 ml.); carbon dioxide was passed through the filtered solution and the precipitate (6 g., 39%) collected by filtration and recrystallised from a large volume of water as needles, m. p. above 380° (Found : C, 51·9; H, 3·3; N, 25·9. Calc. for $C_7H_5O_2N_3$: C, 51·5; H, 3·1; N, 25·8%).

The dihydroxy-compound (500 mg.) was distilled with zinc dust (5 g.). The distillate was dissolved in chloroform, and the solution evaporated to dryness after treatment with charcoal. The residue (50 mg., 14%) was recrystallised from benzene–light petroleum (b. p. 60—80°),

[24] Fox and Gibar, *J. Org. Chem.*, 1952, **17**, 1653.
[25] Gorvin, *J.*, 1949, 3304.
[26] Berrie, Newbold, and Spring, *J.*, 1952, 2042.

affording 1 : 3 : 4-triazaindene, needles, m. p. 152° (Found : C, 60·6; H, 4·2; N, 35·3. Calc. for $C_6H_5N_3$: C, 60·5; H, 4·2; N, 35·3%) (Petrow and Saper [18] give m. p. 153°).

2 : 4-*Dichloro*-1 : 3 : 5-*triazanaphthalene* (II).—(*a*) The following procedure has been found the most reliable : A mixture of 2 : 4-dihydroxy-1 : 3 : 5-triazanaphthalene (5 g.), phosphorus oxychloride (75 ml.), and triethylamine (10 ml.) was heated under reflux for 6 hr. The product was evaporated to dryness under reduced pressure and the residue heated at 100° *in vacuo* for 2 hr. The cooled residue was treated with ice-water (200 ml.), and the insoluble portion collected, dried at the pump, and sublimed at 140°/0·1 mm.; the resulting *dichloro-compound* (3·25 g., 53%), recrystallised from light petroleum (b. p. 80—100°), had m. p. 173° (Found : C, 42·4; H, 1·6; Cl, 35·7. $C_7H_3N_3Cl_2$ requires C, 42·0; H, 1·5; Cl, 35·5%).

(*b*) The same compound has been obtained in 46% yield by refluxing the dihydroxy-compound (500 mg.) for 2 hr. with phosphorus oxychloride (20 ml.) and dimethylaniline (20 ml.). The cooled product was poured on ice, the pH brought to 4—5 and the crude dichloro-compound filtered off and sublimed. The yields obtained by this procedure are variable and very low if larger quantities are used. When diethylaniline was used in place of dimethylaniline the only isolated product (100 mg., 11%) was 2-*chloro*-4-N-*ethylanilino*-1 : 3 : 5-*triazanaphthalene* (III; R = Cl, R′ = NEtPh), pale green leaflets, m. p. 168°, from light petroleum (b. p. 80—100°) (Found : C, 64·0; H, 4·7; N, 19·3; Cl, 11·9. $C_{15}H_{13}N_4Cl$ requires C, 63·3; H, 4·6; N, 19·6; Cl, 12·5%).

1 : 3 : 5-*Triazanaphthalene* (III; R = R′ = H).—2 : 4-Dichloro-1 : 3 : 5-triazanaphthalene (3 g.) was suspended in anhydrous ethanol (100 ml.) and shaken with hydrogen in the presence of Adams catalyst (300 mg.). When hydrogen uptake ceased, the mixture was filtered and the filtrate evaporated to dryness under reduced pressure. All attempts to distil, sublime, or crystallise the residue, which rapidly became red, failed. A portion was extracted with benzene, and the benzene extract treated with light petroleum (b. p. 60—80°); evaporation, under reduced pressure, of the filtrate from the brown amorphous precipitate left a yellow semi-crystalline wax, readily soluble in water, alcohol, and benzene, which resisted further attempts at purification. Addition of aqueous picric acid to the aqueous solution precipitated 1 : 3 : 5-*triazanaphthalene picrate*, which crystallised from water in needles, m. p. 191° (Found : C, 37·2; H, 3·2; N, 20·7. $C_{13}H_9O_7N_6.3H_2O$ requires C, 37·7; H, 3·4; N, 20·3%). Attempted preparation of the hydrochloride from the picrate yielded only red-brown amorphous material.

The same unstable base, yielding the same picrate, was obtained when the hydrogenation was carried out in the presence of magnesium oxide and also by refluxing 2 : 4-dimercapto- and 2 : 4-diethylthio-1 : 3 : 5-triazanaphthalene with Raney nickel in aqueous ethanol.

2 : 4-*Dimercapto*-1 : 3 : 5-*triazanaphthalene* (III; R = R′ = SH).—2 : 4-Dichloro-1 : 3 : 5-triazanaphthalene (500 mg.) and thiourea (2 g.) were refluxed together in dry dioxan (75 ml.) for 5 min. The precipitated dithiuronium salt (700 mg.; m. p. 254°) was separated from the hot solution by filtration, washed with alcohol and ether, and dried at 100°. This salt was heated in water (50 ml.) at 100° for an hour; the cooled solution deposited the *dithiol* (150 mg., 31%) as deep yellow needles, m. p. 340° (decomp.) (Found : C, 43·7; H, 3·0; N, 21·7. $C_7H_5N_3S_2$ requires C, 43·1; H, 2·6; N, 21·5%).

2 : 4-*Diethylthio*-1 : 3 : 5-*triazanaphthalene* (III; R = R′ = SEt).—2 : 4-Dichloro-1 : 3 : 5-triazanaphthalene (500 mg.) was added to sodium ethyl sulphide (from sodium, 150 mg., and ethanethiol, 20 ml.), and the mixture heated under reflux for 6 hr. Evaporation to dryness, under reduced pressure, of the filtered product afforded the *dithio-compound* (500 mg., 80%) which, recrystallised from light petroleum (b. p. 40—60°), had m. p. 56° (Found : C, 52·7; H, 5·4; S, 25·3. $C_{11}H_{13}N_3S_2$ requires C, 52·6; H, 5·2; S, 25·5%).

2 : 4-*Dimethoxy*-1 : 3 : 5-*triazanaphthalene* (III; R = R′ = OMe).—2 : 4-Dichloro-1 : 3 : 5-triazanaphthalene (250 mg.) was added to methanolic sodium methoxide (from sodium, 70 mg., and anhydrous methanol, 15 ml.), and the mixture heated under reflux for 5 hr. The product was evaporated to dryness under reduced pressure and the residue extracted with benzene. Evaporation of the extract afforded the *dimethoxy-compound* (150 mg., 63%), which crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 138° (Found : N, 22·35. $C_9H_9O_2N_3$ requires N, 22·0%).

2 : 4-*Diethoxy*-1 : 3 : 5-*triazanaphthalene* (III; R = R′ = OEt), prepared similarly in 55% yield, crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 110° (Found : C, 60·45; H, 6·2. $C_{11}H_{13}O_2N_3$ requires C, 60·3; H, 5·9%).

1 : 2 : 3 : 4-*Tetrahydro*-1 : 3-*dimethyl*-2 : 4-*dioxo*-1 : 3 : 5-*triazanaphthalene* (IV).—Dimethyl sulphate (3 g.) was shaken with a solution of 2 : 4-dihydroxy-1 : 3 : 5-triazanaphthalene (250 mg.) in 2N-sodium hydroxide (10 ml.). Next day, the solution was basified with aqueous

ammonia and extracted with chloroform. Evaporation of the extract yielded the *N-methyl* derivative (140 mg., 48%), which crystallised from ethanol in needles, m. p. 246° (Found : C, 56·3; H, 4·5. $C_9H_9O_3N_3$ requires C, 56·6; H, 4·7%).

2 : 4-*Diamino*-1 : 3 : 5-*triazanaphthalene* (III; R = R′ = NH_2).—Ammonia was passed for 3 hr. through a boiling solution of 2 : 4-dichloro-1 : 3 : 5-triazanaphthalene (1 g.) in phenol (20 g.). After cooling to 60°, most of the phenol was decanted off from the deposited product; the residue was treated with 10% sodium hydroxide solution and cooled. The *diamine* (200 mg., 25%) was collected, washed with water, and recrystallised from aqueous ethanol, forming plates, m. p. 318° (Found : C, 52·3; H, 4·35; N, 43·2. $C_7H_7N_5$ requires C, 52·15; H, 4·35; N, 43·5%). When boiled with 2N-sodium hydroxide for 30 min. this compound was converted into the dihydroxy-compound (I).

4-*Amino*-2-*chloro*-1 : 3 : 5-*triazanaphthalene* (V).—Ammonia was passed for 10 min. through a solution of 2 : 4-dichloro-1 : 3 : 5-triazanaphthalene (500 mg.) in dry dioxan (50 ml.). The precipitate was dissolved in N-nitric acid and reprecipitated with aqueous ammonia, affording the *base* (350 mg., 78%) which, crystallised from a large volume of water, had m. p. 265° (Found : N, 30·8. $C_7H_5N_4Cl$ requires N, 31·0%). This compound was recovered unchanged after 16 hours' boiling with water but was completely converted into the dihydroxy-compound (I) when boiled with 2N-sodium hydroxide for 30 min.

4-*Amino*-2-*mercapto*-1 : 3 : 5-*triazanaphthalene* (VI).—(*a*) 4-Amino-2-chloro-1 : 3 : 5-triazanaphthalene (700 mg.) and thiourea (700 mg.) were refluxed together in ethanol (50 ml.) for 4 hr. The yellow *amino-thiol* (650 mg., 94%) was collected from the hot mixture by filtration, washed with ethanol, and dried at 100°; a specimen, purified for analysis by dissolution in dilute sodium hydroxide solution and reprecipitation with acetic acid, had m. p. 344° (Found : C, 46·6; H, 3·5. $C_7H_6N_4S$ requires C, 47·1; H, 3·4%).

(*b*) 2 : 4-Dimercapto-1 : 3 : 5-triazanaphthalene (50 mg.) was heated at 100° for 2 hr. with ammonia solution (*d* 0·880; 20 ml.). The precipitated aminomercaptan (40 mg., 88%) was collected and dried at 100°; it formed greenish-yellow needles, m. p. and mixed m. p. 344°.

4-*Amino*-1 : 3 : 5-*triazanaphthalene* (VII).—4-Amino-2-mercapto-1 : 3 : 5-triazanaphthalene (650 mg.) was refluxed for 3 hr. with Raney nickel (3 g.) in ethanol (200 ml.) containing ammonia solution (*d* 0·880; 40 ml.). Evaporation under reduced pressure of the filtered product afforded the *amine* (500 mg., 94%), which crystallised from water in needles, m. p. 224° (Found : C, 57·5; H, 4·1. $C_7H_6N_4$ requires C, 57·5; H, 4·1%).

4-*Hydroxy*-1 : 3 : 5-*triazanaphthalene* (VIII).—(*a*) 4-Amino-1 : 3 : 5-triazanaphthalene (50 mg.), in 5N-hydrochloric acid (8 ml.), was heated at 100° for 30 min. The solution was then concentrated under reduced pressure to 1 ml. and treated with excess of 2N-sodium carbonate. The precipitated hydroxy-compound had m. p. 342°, not depressed on admixture with a specimen prepared by method (*b*).

(*b*) 3-Aminopicolinic acid (13 g.) and formamide (8 g.) were heated together under reflux for 2½ hr. at 130° and then for a further 2½ hr. at 180°. The hydroxy-compound separated on cooling and was recrystallised from water, forming needles, m. p. 346° (9 g., 65%) (Price and Curtin,[1] who obtained only a 31% yield, record m. p. 346°).

2-*Chloro*-4-*diethylamino*-1 : 3 : 5-*triazanaphthalene* (III; R = Cl, R′ = NEt_2).—2 : 4-Dichloro-1 : 3 : 5-triazanaphthalene (150 mg.) and diethylamine (0·25 ml.) were kept at room temperature in anhydrous dioxan (15 ml.) for 15 min. Evaporation of the filtered solution, followed by crystallisation from light petroleum (b. p. 40—60°), afforded the *base* (160 mg., 90%), m. p. 82° (Found : C, 56·6; H, 5·3; N, 23·5. $C_{11}H_{13}N_4Cl$ requires C, 55·8; H, 5·5; N, 23·7%).

2-*Chloro*-4-3′-*diethylaminopropylamino*-1 : 3 : 5-*triazanaphthalene*.—2 : 4-Dichloro-1 : 3 : 5-triazanaphthalene (600 mg.) and 3-diethylaminopropylamine 390 mg.) were refluxed in anhydrous dioxan for 3 hr. On concentration to 10 ml., followed by cooling, the *base hydrochloride* (400 mg., 40%) crystallised and, recrystallised from dioxan and benzene, had m. p. 128° (Found : N, 21·5. $C_{14}H_{21}N_5Cl_2$ requires N, 21·3%).

Action of Hydrazine Hydrate on 2 : 4-*Dichloro*-1 : 3 : 5-*triazanaphthalene*.—Hydrazine hydrate (1 ml.) was added dropwise to the dichloro-compound (500 mg.) in cold dioxan (20 ml.). After 10 minutes' shaking the cream-coloured precipitate was filtered off, washed with ethanol and and ether, and dried *in vacuo*; 2(or 4)-*hydrazino*-4(or 2)-*hydroxy*-1 : 3 : 5-*triazanaphthalene* (300 mg., 68%) crystallised from ethanol in plates, m. p. 385° (decomp.) (Found : N, 39·9. $C_7H_7ON_5$ requires N, 39·6%). Addition of ethanol to the original dioxan filtrate precipitated a small amount of 2 : 4-*dihydrazino*-1 : 3 : 5-*triazanaphthalene*, plates, m. p. 266°, from ethanol (Found : N, 51·2. $C_7H_9N_7$ requires N, 51·3%).

1 : 3 : 8-*Triazanaphthalene derivatives.*

2-Aminonicotinic Acid Derivatives.—The following were prepared from 2-aminonicotinic acid [19] by the procedure described above for their isomerides: ethyl 2-aminonicotinate, leaflets, m. p. 96°, from water (lit.,[37] m. p. 92°) (Found: C, 58·2; H, 6·2. Calc. for $C_8H_{10}O_2N_2$: C, 57·8; H, 6·0%); *2-aminonicotinic hydrazide*, needles, m. p. 176°, from ethyl acetate (Found: N, 36·7. $C_6H_8ON_4$ requires N, 36·8%); *acetone 2-aminonicotinoylhydrazone*, needles, m. p. 179°, from acetone (Found: C, 55·05; H, 6·4. $C_9H_{12}ON_4$ requires C, 55·1; H, 6·3%).

The hydrazone (700 mg.), suspended in water (10 ml.) and ammonia solution (*d* 0·880; 2 ml.), was added to an ice-cold solution of sodium metaperiodate (1·1 g.) in water (15 ml.) and ammonia solution (10 ml.). After 30 minutes' shaking, barium acetate (1·2 g.), in water (5 ml.), was added and the precipitated barium salts were filtered off; the filtrate was brought to pH 7, saturated with sodium chloride, and extracted with ether. Evaporation of the dried extract and crystallisation of the residue from light petroleum (b. p. 60—80°) afforded 2-aminonicotinaldehyde (250 mg., 56%), leaflets, m p. 98° (Found: C, 59·0; H, 4·9; N, 23·2. Calc. for $C_6H_6ON_2$: C, 59·0; H, 4·9; N, 23·0%) (Goldfarb and Karaulova [38] record m. p. 99° for a specimen obtained by ozonolysis of 2-aminometanicotine). Similar periodate oxidation of 2-aminonicotinic hydrazine gave the same compound in 30% yield.

2 : 4-*Dihydroxy*-1 : 3 : 8-*triazanaphthalene* (XII).—A specimen prepared by a method similar to that of Robins and Hitchings [6] had m. p. 361°, not depressed on admixture with a specimen prepared by the method of McLean and Spring.[4]

2 : 4-*Dichloro*-1 : 3 : 8-*triazanaphthalene* (XIII; R = R′ = Cl).—2 : 4-Dihydroxy-1 : 3 : 8-triazanaphthalene (5 g.) was refluxed with phosphorus oxychloride (125 g.) for 6 hr.; the mixture was evaporated to dryness under reduced pressure and the residue heated *in vacuo* at 115° for 30 min. Water (50 ml.), containing sodium hydrogen carbonate (25 g.), was then added; some dichloro-compound was collected by filtration and a further amount extracted from the filtrate with ethyl acetate. The product (2 g., 33%), purified by sublimation at 150° (bath)/10^{-3} mm., had m. p. 160° (McLean and Spring [4] give m. p. 156—157°, and Robins and Hitchings [6] m. p. 158—158·5°).

This compound (500 mg.), suspended in ethanol (50 ml.), was hydrogenated over Adams catalyst, 2 mols. of hydrogen being taken up in 1 hr. Filtration and evaporation yielded 2 : 4-*dichloro*-5 : 6 : 7 : 8-*tetrahydro*-1 : 3 : 8-*triazanaphthalene* (XIV; R = R′ = Cl) (250 mg., 49%), which, purified by sublimation at 130° (bath)/10^{-3} mm., had m. p. 165° (Found: C, 41·9; H, 3·9; N, 20·6. $C_7H_7N_3Cl_2$ requires C, 41·2; H, 3·4; N, 20·6%); the same compound was obtained when the hydrogenation was carried out in the presence of magnesium oxide (500 mg.). The compound was recovered unchanged after 10 minutes' boiling with 10% sodium hydroxide solution but, on refluxing with methanolic sodium methoxide for 5 hr., afforded 5 : 6 : 7 : 8-*tetrahydro*-2 : 4-*dimethoxy*-1 : 3 : 8-*triazanaphthalene* (XIV; R = R′ = OMe), needles, m. p. 166°, from light petroleum (b. p. 60—80°) (Found: N, 21·9. $C_9H_{13}O_2N_3$ requires N, 21·5%).

2 : 4-*Diethylthio*-1 : 3 : 8-*triazanaphthalene* (XIII; R = R′ = SEt).—2 : 4-Dichloro-1 : 3 : 8-triazanaphthalene (300 mg.) was refluxed for 6 hr. with sodium ethyl sulphide (from sodium, 100 mg., and ethanethiol, 15 ml.). Filtration, evaporation, and crystallisation from light petroleum (b. p. 40—60°) afforded the *thio-compound* (quantitative yield), m. p. 76° (Found: C, 52·9; H, 5·3; S, 25·4. $C_{11}H_{15}N_3S_2$ requires C, 52·6; H, 5·2; S, 25·5%).

2 : 4-*Diamino*-1 : 3 : 8-*triazanaphthalene* (XIII; R = R′ = NH_2), prepared in 72% yield as described for the 1 : 3 : 5-compound (p. 1052), crystallised from aqueous ethanol in needles, m. p. 342° (Found: N, 43·1. Calc. for $C_7H_7N_5$: N, 43·5%) (Robins and Hitchings [6] record m. p. 356°).

4-*Amino*-2-*chloro*-1 : 3 : 8-*triazanaphthalene* (XIII; R = Cl; R′ = NH_2), also prepared in the same manner as its 1 : 3 : 5-analogue, had m. p. above 360° (Found: N, 31·35. $C_7H_5N_4Cl$ requires N, 31·0%).

4-*Hydroxy*-2-*mercapto*-1 : 3 : 8-*triazanaphthalene* (XIII; R = SH, R′ = OH).—This compound was prepared by a procedure similar to method (A) of Robins and Hitchings [6] and purified by sublimation at 180° (bath)/10^{-4} mm.; the product (250 mg., 10%) had m. p. 360° (Found: N, 23·9. Calc. for $C_7H_5ON_3S$: N, 23·5%) (Robins and Hitchings [6] give m. p. 355—356°).

4-*Hydroxy*-1 : 3 : 8-*triazanaphthalene* (XIII; R = H, R′ = OH).—(*a*) A specimen prepared by a procedure similar to that of Robins and Hitchings [6] and recrystallised from aqueous methanol,

[37] Dornow and Karlson, *Ber.*, 1940, **73**, 542.
[38] Goldfarb and Karaulova, *J. Gen. Chem.* (*U.S.S.R.*), 1948, **18**, 117.

had m. p. 255—256° (Found: C, 56·9; H, 3·6; N, 28·7. Calc. for $C_7H_5ON_3$: C, 57·2; H, 3·4; N, 28·6%) (Robins and Hitchings [6] give m. p. 255—257°).

(*b*) Raney nickel (5 g.) was added to a solution of 4-hydroxy-2-mercapto-1 : 3 : 8-triazanaphthalene (200 mg.) in 2N-sodium hydroxide (50 ml.). After 16 hr., with occasional shaking, the mixture was filtered and the filtrate saturated with carbon dioxide; the precipitated phenol (50 mg., 30%) had m. p. 255°, not depressed with a specimen prepared by method (*a*).

3-*Aminoisonicotinic hydrazide*, prepared in 89% yield from 3-amino*iso*nicotinic acid [39] as described for its isomerides, crystallised from ethanol in feathery needles, m. p. 187° (Found: N, 36·9. $C_6H_8ON_4$ requires N, 36·8%).

Our thanks are offered to Messrs. V. V. Manohin and F. H. Oliver for the microanalyses and to Dr. A. R. Thompson for the light-absorption measurements. We are also indebted to The Anchor Chemical Company (V.O.) and to the Ministry of Education and the Cumberland Education Committee (R. P.) for maintenance allowances.

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[39] Gabriel and Colman, *Ber.*, 1902, **35**, 2832.

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217. *Steroids and Walden Inversion. Part XXVII.* 3α-Cholesterylamine and Coprostan-3α-ylamine.*

By H. C. Richards, C. W. Shoppee, J. C. P. Sly, and G. H. R. Summers.

Cholest-5-ene-3α-carboxylic acid, as its azide, undergoes the Curtius rearrangement to give the 3α-*iso*cyanate, which by acid hydrolysis yields 3α-cholesterylamine. Reduction of the 3α-*iso*cyanate with lithium aluminium hydride affords *N*-methyl-3α-cholesterylamine, methylated to *NN*-dimethyl-3α-cholesterylamine, which is also obtained by Emde degradation of benzyldimethyl-3α-cholesterylammonium iodide.

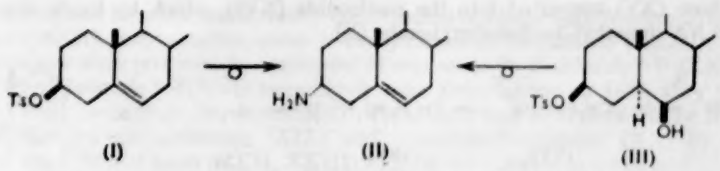
Catalytic hydrogenation of cholest-5-ene-3α-carboxylic acid gives coprostane-3α-carboxylic acid, converted by Curtuis rearrangement of its azide into 3α-acetamidocoprostane, also obtained by hydrogenation of 3α-acetamidocholest-5-ene.

In a re-investigation of the reaction of cholesteryl toluene-*p*-sulphonate (I) with liquid ammonia, Haworth, McKenna, and Powell [1] and Haworth, Lunts, and McKenna [2] isolated three isomeric bases, namely, 3β-cholesterylamine, m. p. 96°, $[\alpha]_D$ −26°, −34°, 3 : 5-*cyclo*cholestan-6β-ylamine,[3] m. p. 84°, $[\alpha]_D$ +34°, +36°, and 3α-cholesterylamine (II) [which Pierce *et al.*[4] prepared by degradation of *N*-benzyl-3α-cholesterylamine by the procedure of Vavasour, Bolker, and McKay,[5] and by ammonolysis and subsequent dehydration of 6β-hydroxycholestan-3α-yl toluene-*p*-sulphonate (III)].

3α-Cholesterylamine (II) has recently been isolated through its *iso*propylidene derivative by Haworth, Lunts, and McKenna,[2] and we have now prepared it in the following way. Cholest-5-ene-3α-carboxylic acid (V; R = H), in which the configuration of the carboxyl group has been established by Roberts, Shoppee, and Stephenson,[6] was converted by thionyl chloride into the chloride, which with dry sodium azide in anhydrous acetone–dioxan gave the azide (IV). This by the Curtius rearrangement, in which configuration in the migrating group is known to be preserved, furnished the 3α-*iso*cyanate (VIII), which

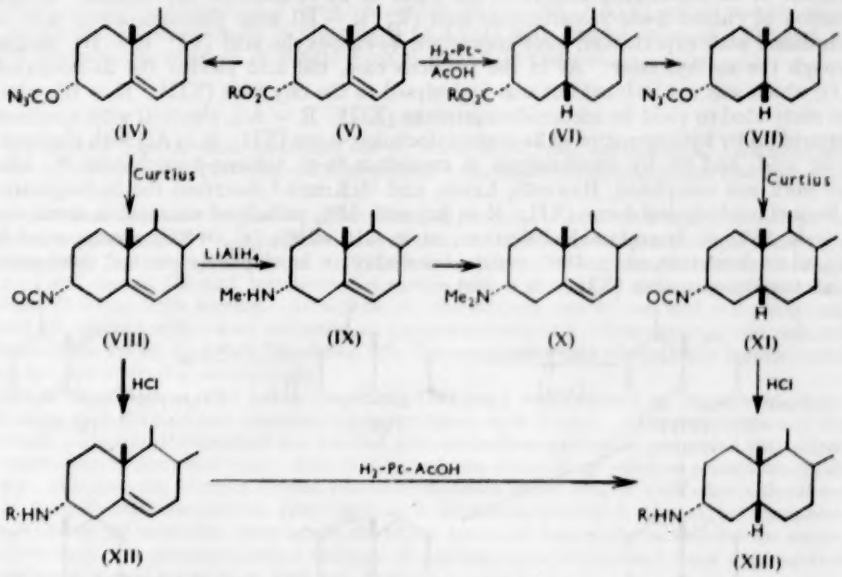
* Part XXVI, *J.*, 1955, 2876.

[1] Haworth, McKenna, and Powell, *J.*, 1953, 1110.
[2] Haworth, Lunts, and McKenna, *J.*, 1955, 986.
[3] Julian, Magnani, Cole, and Meyer, *J. Amer. Chem. Soc.*, 1948, **70**, 1834.
[4] Pierce, Richards, Shoppee, Stephenson, and Summers, *J.*, 1955, 694.
[5] Vavasour, Bolker, and McKay, *Canad. J. Chem.*, 1952, **30**, 933.
[6] Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705.



(I) (II) (III)

(II): m. p. 100°, $[\alpha]_D$ −40°, −44° (ref. 1, 2).



(IV) (V) (VI) (VII)

(VIII) (IX) (X) (XI)

(XII) (XIII)

Formula	M. p.	[α]	Ref.
(V): R = H	155°	−40°	4
R = Me	114	−40	4
(IX)	85—86	−31	*a*
	86		1
	88	−28	7
(XII): R = H	100	−44	2
	100	−40	4
R = Ac	188	−32	*a*
	182		2
	189		5
	189	−30	4

Formula	M. p.	[α]	Ref.
(VI): R = H	179°	+31°	*a*
R = Me	72	+30	*a*
(X)	69	−31	*a*
	71		1
	69		2
	70	−31	8
(XIII): R = Ac	217	+48	*a*
	180		2

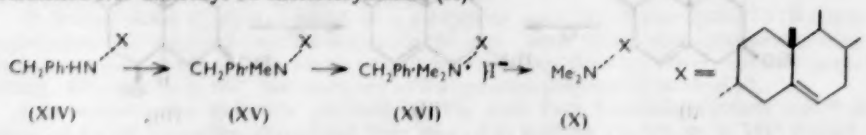
Ref. (*a*) = This work.

could not satisfactorily be purified. The crude 3α-*iso*cyanate, on hydrolysis with hydrochloric acid in benzene–acetic acid, gave 3α-cholesterylamine (XII; R = H) as a colourless oil, which crystallised only with great difficulty and was converted into 3α-acetamidocholest-5-ene (XII; R = Ac).

Reduction of the crude 3α-*iso*cyanate (VIII) with lithium aluminium hydride gave *N*-methyl-3α-cholesterylamine (IX), corresponding with the product prepared from cholesteryl toluene-*p*-sulphonate and monomethylamine by Haworth, McKenna, and Powell [1] and Pierce, Shoppee, and Summers.[7] Methylation gave *NN*-dimethyl-3α-cholesterylamine [8] (X), which was also obtained by the following route: *N*-Benzyl-3α-cholesterylamine [5] (XIV) was methylated with formaldehyde–formic acid, and the

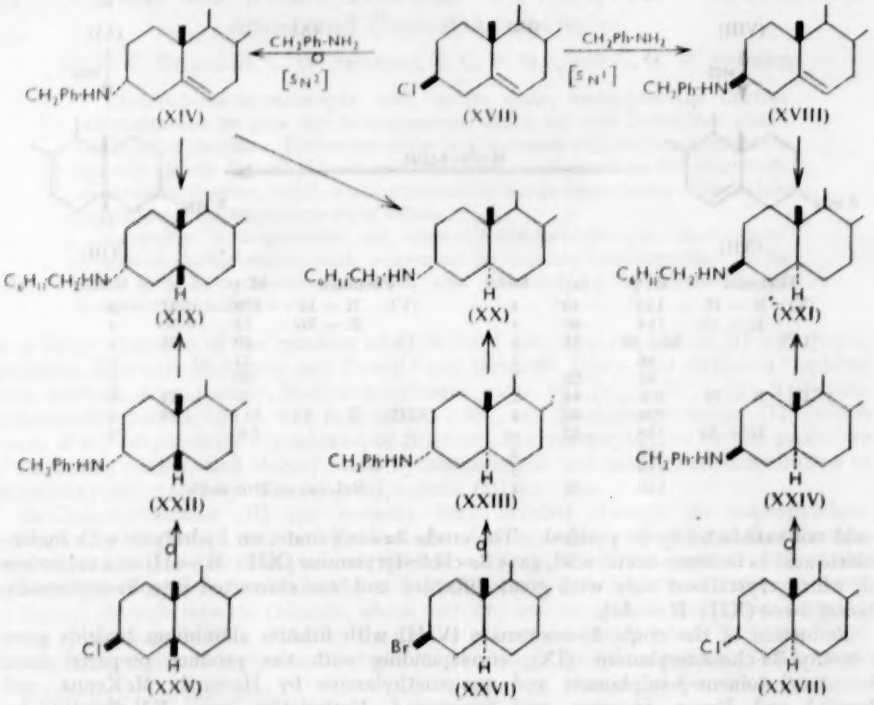
[7] Pierce, Shoppee, and Summers, *J.*, 1955, 690.
[8] Labler, Czerny, and Sorm, *Chem. Listy*, 1954, **48**, 1058.

tertiary base (XV) converted into the methiodide (XVI), which by Emde degradation furnished *NN*-dimethyl-3α-cholesterylamine (X).



(XIV) (XV) (XVI) (X)

It has been shown by Lewis and Shoppee [9] for a variety of substituents that hydrogenation of 3α-substituted cholest-5-enes leads to 3α-substituted coprostanes. Hydrogenation of cholest-5-ene-3α-carboxylic acid (V; R = H) with platinum–acetic acid, in accordance with expectation, gave coprostane-3α-carboxylic acid (VI; R = H), purified through the methyl ester. As in the previous case, the acid yielded the 3α-*iso*cyanate (XI), which was not isolated but was hydrolysed to the oily base (XIII; R = H), which was acetylated to yield 3α-acetamidocoprostane (XIII; R = Ac), identical with specimens prepared (*a*) by hydrogenation of 3α-acetamidocholest-5-ene (XII; R = Ac) with platinum–acetic acid, and (*b*) by ammonolysis of coprostan-3β-yl toluene-*p*-sulphonate.[10] After this work was completed, Haworth, Lunts, and McKenna [2] described the hydrogenation of 3α-acetamidocholest-5-ene (XII; R = Ac) with 15% palladised charcoal in acetic acid to yield 35% of 3α-acetamidocholestane, m. p. 215—216°, $[\alpha]_D$ +33°, accompanied by 46% of an isomeride, m. p. 180°, which is probably an incompletely purified specimen of 3α-acetamidocoprostane (XIII; R = Ac).



(XIV) (XVII) (XVIII)
(XIX) (XX) (XXI)
(XXII) (XXIII) (XXIV)
(XXV) (XXVI) (XXVII)

Some years ago we examined the hydrogenation with platinum oxide in acetic acid of the epimeric *N*-benzyl-3α- (XIV) and -3β-cholesterylamine (XVIII) derived from cholesteryl

[9] Lewis and Shoppee, *J.*, 1955, 1365.
[10] Evans, Shoppee, and Summers, unpublished work.

chloride (XVII) and benzylamine at 180°; the expected products were *N*-benzylcoprostan-3α-ylamine (XXII) and, possibly, some *N*-benzylcholestan-3α-ylamine (XXIII). When these substances were prepared by treatment of coprostan-3β-yl chloride [9,11] (XXV) and cholestan-3β-yl bromide [6] (XXVI) respectively with benzylamine at 180°, they did not correspond with the hydrogenation products. These have now been shown to be *N*-(*cyclo*hexylmethyl)-coprostan-3α-ylamine (XIX) and -cholestan-3α-ylamine (XX) by hydrogenation of the *N*-benzyl bases (XXII, XXIII) with Adams catalyst in acetic acid.

In a similar way, *N*-benzyl-3β-cholesterylamine (XVIII) by hydrogenation with platinum oxide–acetic acid yields *N*-(*cyclo*hexylmethyl)cholestan-3β-ylamine (XXI), also produced by hydrogenation of *N*-benzylcholestan-3β-ylamine (XXIV), which was obtained by treatment of cholestan-3α-yl chloride [12] (XXVII) with benzylamine at 180° and by Wolff–Kishner reduction of *N*-benzyl-6-oxocholestan-3β-ylamine.

Experimental

For general experimental directions see *J.*, 1955, 2876. $[\alpha]_D$ are in $CHCl_3$. Alumina was Spence type H, 200 mesh, activity ~II, neutralised when necessary by Reichstein and Shoppee's procedure.[13]

Cholest-5-en-3α-yl iso*Cyanate*.—Cholest-5-ene-3α-carboxylic acid (500 mg.), dissolved in benzene, was refluxed with thionyl chloride (0·8 c.c.) for 2 hr.; complete evaporation in a vacuum gave the crude chloride as a sticky solid. The chloride, dissolved in dry acetone (35 c.c.) and dioxan (15 c.c.), was treated dropwise with a solution of sodium azide (200 mg.) in water (1·5 c.c.) with stirring. After 0·25 hr., the mixture was diluted and the precipitate filtered off, washed with water, and dried in a vacuum-desiccator. This material was refluxed in benzene for 1·5 hr. to ensure conversion into the *iso*cyanate; the product was a sticky solid which did not crystallise satisfactorily.

3α-*Cholesterylamine*.—The crude *iso*cyanate (200 mg.) was refluxed in benzene for 2 hr. with acetic acid (28 c.c.) and concentrated hydrochloric acid (7 c.c.). After evaporation of the solvent in a vacuum the product was basified with 4N-sodium hydroxide, extracted with ether, and worked up in the usual way. The oil obtained was chromatographed on aluminium oxide (15 g.). Elution with benzene yielded non-basic material whilst elution with ether–chloroform (1 : 1) gave 3α-cholesterylamine (100 mg.) as a colourless oil which tended to crystallise. Acetylation of the base with ether–acetic anhydride furnished 3α-acetamidocholest-5-ene which, after filtration of a pentane solution through aluminium oxide, crystallised from ethyl acetate as needles, m. p. and mixed m. p. 188°, $[\alpha]_D$ −32°.

N-*Methyl*-3α-*cholesterylamine*.—The crude *iso*cyanate (400 mg.), in ether, was treated with lithium aluminium hydride (100 mg.), heated under reflux for 2 hr., cooled, and carefully diluted with water. The precipitated aluminium hydroxide was filtered off, and the ethereal solution washed, dried, and evaporated to furnish an oil (390 mg.). The product was chromatographed on aluminium oxide (12 g.). Elution successively with benzene–pentane (1 : 19; 4 × 40 c.c.), benzene and benzene–ether (1 : 1) gave *N*-methyl-3α-cholesterylamine (270 mg.) which crystallised from acetone in needles, m. p. 85—86°, $[\alpha]_D$ −31° (*c*, 0·8). Methylation with formaldehyde and formic acid gave *NN*-dimethyl-3α-cholesterylamine, m. p. 69°, $[\alpha]_D$ −31° (*c*, 1·0).

NN-*Dimethyl*-3α-*cholesterylamine*.—*N*-Benzyl-3α-cholesterylamine (750 mg.) in formic acid (5 c.c.) and 40% aqueous formaldehyde (7 c.c.) was heated for 4 hr. at 100°. The solution was poured into water and basified with ammonia, the base was extracted with ether, and the ethereal extract washed with water, dried (Na_2SO_4) and evaporated, to yield *N*-benzyl-*N*-methyl-3α-cholesterylamine. This oil was refluxed in acetone (25 c.c.) with methyl iodide (0·5 c.c.) for 2 hr. Evaporation of the solvent, after washing with ether, yielded the *methiodide*, m. p. 220—230° (Found: C, 68·7; H, 8·7. $C_{35}H_{58}NI$ requires C, 68·5; H, 9·2%).

The methiodide (400 mg.) in aqueous ethanol (60 c.c.; 84% EtOH) was vigorously stirred with 2% sodium amalgam (20 g.) added during 8 hr. The solution was decanted, diluted with water, and extracted with ether. Evaporation of the ether gave a solid which after nitration of a pentane solution through aluminium oxide gave *NN*-dimethyl-3α-cholesterylamine, which crystallised from acetone as needles, m. p. and mixed m. p. 66—69°.

[11] Bridgwater and Shoppee, *J.*, 1953, 1709.
[12] Shoppee, *J.*, 1946, 1138.
[13] Reichstein and Shoppee, *Discuss. Faraday Soc.*, 1949, **7**, 205.

Coprostane-3α-carboxylic Acid.—Cholest-5-ene-3α-carboxylic acid (400 mg.), dissolved in acetic acid (200 c.c.), was shaken with platinum oxide (800 mg.) in an atmosphere of hydrogen. Hydrogenation was complete in 3 hr. After filtration the solution was diluted with water and extracted with ether. After working up in the usual way, the ethereal extract furnished a solid which crystallised from aqueous acetone as needles, m. p. 163—174°. The impure acid was esterified with diazomethane, and the oily ester chromatographed on neutralised aluminium oxide (15 g.). Successive elution with pentane–benzene (19 : 1; 8 × 50 c.c.) (9 : 1; 6 × 50 c.c.) (17 : 3; 4 × 50 c.c.) furnished *methyl coprostane-3α-carboxylate* (290 mg.) which crystallised from ether–methanol as needles, m. p. 71—72°, $[\alpha]_D$ +30° (*c*, 1·1) [Found (after drying at 20°/0·03 mm. for 8 hr.): C, 81·2; H, 11·6. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%].

Hydrolysis of methyl coprostane-3α-carboxylate with 2N-ethanolic potassium hydroxide gave *coprostane-3α-carboxylic acid* which crystallised from aqueous acetone as needles, m. p. 179°, $[\alpha]_D$ +31° (*c*, 1·0) [Found (after drying at 20°/0·03 mm.): C, 80·7; H, 11·6. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%].

3α-*Acetamidocoprostane.*—Coprostane-3α-carboxylic acid (200 mg.) was refluxed in benzene with thionyl chloride (1 c.c.) for 2 hr. Evaporation in vacuum gave the crude chloride. The chloride, in dry acetone (25 c.c.) and dioxan (5 c.c.), was treated with sodium azide (100 mg.) in water (1 c.c.). After 15 min. the mixture was diluted with water and extracted with benzene and chloroform, and after working up in the usual way yielded a semisolid residue. This was refluxed in benzene for 1·5 hr. Acetic acid (10 c.c.) and concentrated hydrochloric acid (4 c.c.) were added and the mixture heated for a further 2 hr. The solvent was removed in a vacuum, the hydrochloride basified with ethanolic potassium hydroxide solution, and the product worked up in the usual way. The resultant oil was acetylated with ether–acetic anhydride and the acetyl derivative chromatographed on aluminium oxide (3 g.). Elution with benzene gave 3α-*acetamidocoprostane* (110 mg.), which crystallised from acetone as plates, m. p. 217—218°, mixed m. p. 216—218° [Found (after drying at 100°/0·01 mm.): C, 80·9; H, 11·9. $C_{29}H_{51}ON$ requires C, 81·0; H, 11·95%].

N-*Benzylcoprostan-3α-ylamine.*—3β-Chlorocoprostane (230 mg.) in benzylamine (5 c.c.) was refluxed for 14 hr. The usual working up yielded an oil (300 mg.), which was chromatographed on aluminium oxide (8 g.). Elution with pentane gave an oil (100 mg.), and benzene–pentane also gave oils (total, 90 mg.), whereafter ether–benzene gave oils (total, 30 mg.); the benzene–pentane fractions, $[\alpha]_D$ +30° (*c*, 1·20), did not crystallise but on treatment with hydrochloric acid gave N-*benzylcoprostan-3α-ylamine hydrochloride*, m. p. 136—140°, $[\alpha]_D$ +24° (*c*, 0·87) [Found (after drying at 20°/0·03 mm. for 16 hr.): C, 78·9; H, 10·9. $C_{34}H_{54}NCl$ requires C, 79·4; H, 11·0%].

N-*Benzylcholestan-3α-ylamine.*—3β-Bromocholestane (100 mg.) in benzylamine (10 c.c.) was refluxed for 18 hr. Working up in the usual way previously described gave an oil (80 mg.) which was chromatographed on aluminium oxide (5 g.). Elution with pentane–benzene (4 : 1) gave an oil (50 mg.) which solidified and on crystallisation from acetone yielded N-*benzylcholestan-3α-ylamine*, m. p. 75—77°, $[\alpha]_D$ +27° (*c*, 1·14) [Found (after drying at 20°/0·03 mm. for 3 hr.): C, 85·4; H, 11·4. $C_{34}H_{55}N$ requires C, 85·5; H, 11·6%]. Elution with benzene–ether (9 : 1) yielded a few mg. of a solid, which crystallised from acetone as plates, m. p. 113—114°, $[\alpha]_D$ 16° (*c*, 0·71), undepressed on admixture with *N*-benzylcholestan-3β-ylamine (*vide infra*).

N-(cyclo*Hexylmethyl*)*cholestan-3α-ylamine and* N-(cyclo*Hexylmethyl*)*coprostan-3α-ylamine.*—*N*-Benzyl-3α-cholesterylamine (500 mg.) in glacial acetic acid (20 c.c.) was hydrogenated in the presence of platinum oxide (100 mg.); after 3 hr. four mols. of hydrogen were absorbed. Working up in the usual way yielded an oil (450 mg.) which was chromatographed on aluminium oxide (14 g.). Elution with pentane–benzene (9 : 1) gave a sticky solid (90 mg.) which on crystallisation from acetone gave N-(cyclo*hexylmethyl*)*cholestan-3α-ylamine* as plates, m. p. 114—115°, $[\alpha]_D$ +19° (*c*, 0·75) [Found (after drying at 20°/0·03 mm. for 3 hr.): C, 84·1; H, 12·3. $C_{34}H_{61}N$ requires C, 84·4; H, 12·7%]. Elution with pentane–benzene (4 : 1) yielded oils (80 mg.) and pentane–benzene (1 : 1) and benzene gave an oil (200 mg.), $[\alpha]_D$ +31° (*c*, 1·30). This fraction formed N-(cyclo*hexylmethylcoprostan*)-3α-*ylamine hydrochloride*, m. p. 238—242°, $[\alpha]_D$ +17° (*c*, 0·67) [Found (after drying at 20°/0·03 mm. for 16 hr.): C, 78·6; H, 11·85. $C_{34}H_{62}NCl$ requires C, 78·5; H, 12·0%].

N-(cyclo*Hexylmethyl*)*cholestan-3α-ylamine.*—*N*-Benzylcholestan-3α-ylamine (50 mg.) in glacial acetic acid (5 c.c.) was hydrogenated in the presence of platinum oxide (20 mg.). Isolation of the product in the usual way and crystallisation from acetone gave plates, m. p. 114—115°, $[\alpha]_D$ +21° (*c*, 0·84), undepressed by the specimen in the previous experiment.

N-(cyclo*Hexylmethyl*)*coprostan-3α-ylamine.*—*N*-Benzylcoprostan-3α-ylamine (50 mg.) on

hydrogenation yielded an oil which formed a hydrochloride, m. p. 240°, $[\alpha]_D$ +16° (*c*, 0·66), undepressed on admixture with the hydrochloride obtained from the reduction of *N*-benzyl-3α-cholesterylamine.

N-Benzylcholestan-3β-ylamine.—(*a*) 3α-Chlorocholestane (700 mg.) in benzylamine (10 c.c.) was refluxed for 14 hr. Dilution with 2N-hydrochloric acid gave *N*-benzylcholestan-3β-ylamine hydrochloride, which after filtration, washing with water, and basification with ammonia, was extracted with ether. The ethereal extract yielded an oil (700 mg.), which was chromatographed on aluminium oxide (20 g.). Elution with pentane gave cholest-2-ene (300 mg.; m. p. 68°). Elution with benzene–ether (9 : 1) yielded *N-benzylcholestan-3β-ylamine* (150 mg.) which crystallised from acetone as plates, m. p. 114—115°, $[\alpha]_D$ +19° (*c*, 0·87) [Found (after drying at 20°/0·03 for 2 hr.): C, 85·75; H, 11·4. $C_{34}H_{55}N$ requires C, 85·5; H, 11·6%].

(*b*) *N*-Benzyl-6-oxocholestan-3β-ylamine (500 mg.) in ethanol (20 c.c.) was refluxed for 0·5 hr. with hydrazine hydrate (4 c.c.) and potassium hydroxide (2 g.). Ethylene glycol (20 c.c.) was added and the refluxing continued for 3 hr. at 200°. The mixture was diluted with water, extracted with ether, and worked up in the usual way to yield an oil, which on crystallisation from ethyl acetate gave plates, m. p. 116—117°, undepressed by the above specimen.

N-(cycloHexylmethyl)cholestan-3β-ylamine.—(*a*) *N*-Benzyl-3β-cholesterylamine (350 mg.) in glacial acid (20 c.c.) was hydrogenated in the presence of platinum oxide (100 mg.). After 1 hr., the solution was poured into water and extracted with ether, and the ethereal extract washed with ammonia. Working up in the usual way gave a white solid, which on crystallisation from ethyl acetate gave N-(cyclo*hexylmethyl*)*cholestan-3β-ylamine* as neeedles, m. p. 143—145°, $[\alpha]_D$ +16° (*c*, 0·82) [Found (after drying at 20°/0·02 mm. for 3 hr.): C, 84·4; H, 12·7; N, 2·9. $C_{34}H_{61}N$ requires C, 84·4; H, 12·7; N, 2·9%].

(*b*) *N*-Benzylcholestan-3β-ylamine (200 mg.) in glacial acetic acid (20 c.c.) was hydrogenated in the presence of platinum oxide (80 mg.). After 2·5 hr. 3 mols. of hydrogen had been absorbed. Working up in the usual way gave *N*-(*cyclo*hexylmethyl)cholestan-3β-ylamine which crystallised from acetone as needles, m. p. 146—148°, $[\alpha]_D$ +18° (*c*, 0·79), undepressed on admixture with the above specimen.

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University of Wales, University College, Swansea. [*Received, September 14th*, 1955.]

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218. *Steroids and Walden Inversion. Part XXVIII.* The Structure of the Lactonic Acid derived from 6α-Hydroxy-2 : 3-secocholestane-2 : 3-dioic Acid.*

By D. R. James and C. W. Shoppee.

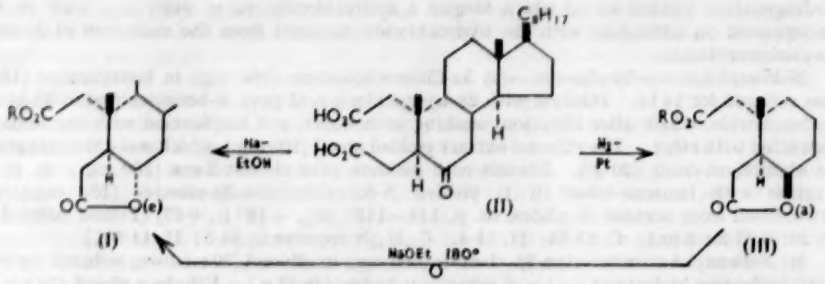
The lactonic acid, m. p. 202°, $[\alpha]_D$ −20°, derived from 6α-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioic acid, is shown to be a 3→6α-γ-lactone (I; R = H) and not a 2→6α-δ-lactone (IV; R = H).

In Part VIII Shoppee and Summers [1] examined the capacity for lactonisation of the epimeric 6-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioic acids. It was found that 6-oxo-2 : 3-*seco*-cholestane-2 : 3-dioic acid (II) by reduction with sodium–ethanol gave a compound regarded as the 3→6α-γ-lactonic acid (I; R = H), whilst hydrogenation with platinum in acetic acid or ethanol gave the 3→6β-γ-lactonic acid (III; R = H), convertible into the isomeride (I; R = H) by treatment with sodium ethoxide at 180°.

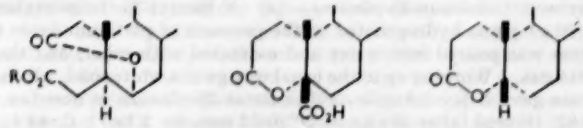
In a letter dated October 31st, 1952, Dr. A. Georg (Geneva) suggested that the evidence did not exclude a 2→6α-δ-lactonic acid structure (IV; R = H) for the compound, m. p. 202°, $[\alpha]_D$ −20°, and quoted as examples of stable steroid δ-lactones those of 5-hydroxy-3 : 4-*seco*cholestane-3 : 4-dioic acid [2] (V) and 5-hydroxy-3 : 5-*seco*-A-norcholestan-3-oic acid [3] (VI).

* Part XXVII, preceding paper.

[1] Shoppee and Summers, *J.*, 1952, 3374.
[2] Tschesche, *Ber.*, 1932, **65**, 185.
[3] Salamon, *Z. physiol. Chem.*, 1941—2, **272**, 61.



R	Formula	M. p.	$[\alpha]_D$	R	Formula	M. p.	$[\alpha]_D$
H	(I)	202°	−20°	H	(III)	196°	+58°
Me	(I)	99	−19	Me	(III)	99	+59



(IV) (V) (VI)

6α-Hydroxy-2 : 3-*seco*cholestane-2 : 3-dioic acid is not comparable with natural steroids because ring A has been broken, so that $C_{(5)}$, $C_{(6)}$, $C_{(7)}$, and $C_{(10)}$ have mobility comparable with that admitted for $C_{(1)}$, $C_{(2)}$, $C_{(3)}$, and $C_{(4)}$ in *trans*-decalin, and ring B can undergo strainless transition into a boat form. Examination of molecular models shows that there are two possible conformations of ring B as a boat form, that with ends at $C_{(6)}$ and $C_{(9)}$ (Fig. 1) and that with ends at $C_{(5)}$ and $C_{(8)}$ (Fig. 2). In both conformations 2→6β-δ-lactone formation with C–C and C–O bonds of normal length appears impossible, whilst 3→6β-γ-lactone formation involves only slight strain. In both conformations 3→6α-γ-lactone formation with bonds of normal length appears impossible, but in the second conformation (Fig. 2) a 2→6α-δ-lactone can be formed virtually without strain (Fig. 3).

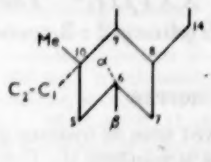


Fig. 1

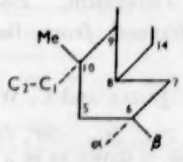


Fig. 2

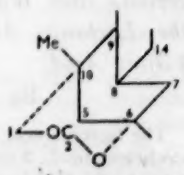
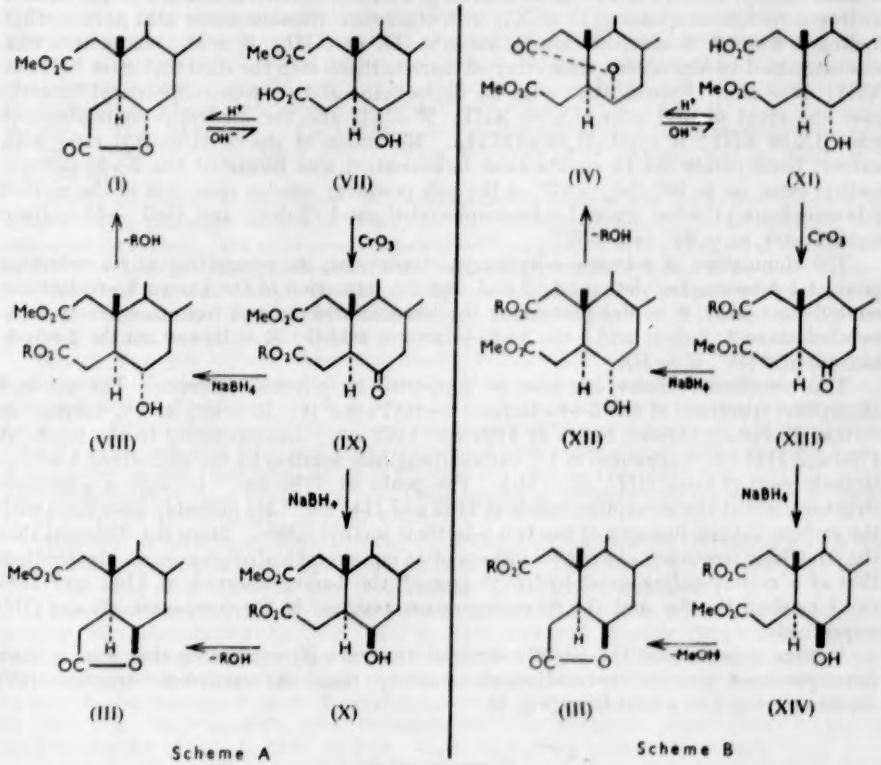


Fig. 3

In view of the usual equilibrium between an acid and its lactone it might be possible for the slightly strained 3→6α-γ-lactonic acid (I; ring B in chair form) to pass into the strainless 2→6α-δ-lactonic acid (IV; ring B in boat form). It seemed desirable to attempt to ascertain the structure of the lactonic acid, m. p. 202°, $[\alpha]_D$ −20°, and it appeared possible to reach an experimental decision between formulæ (I) and (IV) in the following way.

If the lactonic methyl ester, m. p. 99°, $[\alpha]_D$ −19°, has structure (I; R = Me), treatment with one equivalent of sodium hydroxide should open the lactone ring, and oxidation of the resulting methyl hydrogen ester (VII) should yield 2-methyl 3-hydrogen 6-oxo-2 : 3-*seco*-cholestane-2 : 3-dioate (IX; R = H), convertible, *e.g.*, with diazoethane, into the 3-ethyl 2-methyl ester (IX; R = Et). Reduction of this ester with sodium borohydride should give 3-ethyl 2-methyl 6β-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioate (X), possibly accompanied by the 6α-hydroxy-epimeride (VIII), which by spontaneous lactonisation should yield, with elimination of ethanol and methanol respectively, the *known* 3→6β-lactonic methyl ester (III; R = Me) and the starting material (I; R = Me).

If, however, the lactonic methyl ester, m. p. 99°, $[\alpha]_D$ −19°, has structure (IV; R = Me), ring fission with one equivalent of sodium hydroxide should give 3-methyl 2-hydrogen 6α-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioate (XI), which, by oxidation should afford 3-methyl 2-hydrogen 6-oxo-2 : 3-*seco*cholestane-2 : 3-dioate (XIII; R = H), giving the unsymmetrical 2-ethyl 3-methyl ester (XIII; R = Et). Sodium borohydride reduction should



now furnish 2-ethyl 3-methyl 6β-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioate (XIV; R = Et), with possibly some of the 6α-hydroxy-epimer (XII; R = Et), which by spontaneous lactonisation should yield, with elimination of methanol and ethanol respectively, the *unknown* 3→6β-lactonic ethyl ester (III; R = Et) and the starting material (IV; R = Me).

Experimentally, titration of the lactonic methyl ester (I or IV; R = Me) with one equivalent of sodium hydroxide at ~60° and treatment with potassium permanganate gave a product, m. p. 167—169°, $[\alpha]_D$ +12°, which was at first regarded as methyl hydrogen 6-oxo-2 : 3-*seco*cholestane-2 : 3-dioate (VII or XI); treatment with ethereal diazoethane gave a non-crystalline product, which by chromatography yielded only the starting material and by treatment with sodium borohydride and chromatography also furnished only the starting material. Attempts to prepare the lactonic ethyl esters (I or IV; R = Et) and (III; R = Et) by using ethereal diazoethane failed to give crystalline products, although by using the same diazoethane solution ethyl cholest-5-ene-3β-carboxylate,[4] m. p. 83°, was formed without difficulty. Finally, it was discovered that treatment of the lactonic methyl ester (I or IV; R = Me) with one equivalent of sodium hydroxide at ~60° for 5

[4] Marker, Oakwood, and Crooks, *J. Amer. Chem. Soc.*, 1936, **58**, 481.

min. and acidification in the cold with 2N-sulphuric acid gave the compound, m. p. 167—169°, $[\alpha]_D$ +12°. This is therefore 2-methyl 3-hydrogen (VII) or 3-methyl 2-hydrogen 6α-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioate (XI), and appears to resist mild oxidation by permanganate; hydrolysis with hot ethanolic potassium hydroxide gave the lactonic acid (I or IV; R = H), m. p. 202°, $[\alpha]_D$ −20°, converted by ethereal diazomethane into the lactonic methyl ester (I or IV; R = Me), m. p. 99°, $[\alpha]_D$ −19°. Oxidation of the methyl hydrogen 6α-hydroxy-ester (VII or XI) with chromium trioxide–acetic acid gave methyl hydrogen 6-oxo-2 : 3-*seco*cholestane-2 : 3-dioate (IX or XIII; R = H), whose structure was confirmed by conversion with ethereal diazomethane into the dimethyl ester [5] (IX = XIII; R = Me). Esterification with (*a*) diazoethane and (*b*) *p*-bromophenacyl bromide gave the ethyl methyl ester (IX or XIII; R = Et) and the methyl *p*-bromophenacyl ester (IX or XIII; R = *p*-$C_6H_4Br{\cdot}CO{\cdot}CH_2$). Reduction of the ethyl methyl ester with sodium borohydride led to spontaneous lactonisation and furnished the 3→6β-lactonic methyl ester, m. p. 99°, $[\alpha]_D$ +57°, as the sole product; similar reduction of the methyl *p*-bromophenacyl ester gave 1-*p*-bromophenylethane-1 : 2-diol, and the3 →6β-lactonic methyl ester, m. p. 99°, $[\alpha]_D$ +57°.

The elimination of *p*-bromo-ω-hydroxyacetophenone, its recognition as its reduction product 1-*p*-bromophenylethane-1 : 2-diol, and the formation of the known 3→6β-lactonic methyl ester (III; R = Me) prove that the lactonic acid derived from 6α-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioic acid is the 3→6α-γ-lactonic acid (I; R = H) and not the 2→6α-δ-lactonic acid (IV : R = H).

This chemical evidence can now be supported by physical evidence. The infrared absorption spectrum of the 3→6α-lactonic methyl ester (I; R = Me) in 1% solution in carbon disulphide showed bands at 1780 and 1162 cm.$^{-1}$ corresponding to the bands at 1780 and 1145 cm.$^{-1}$ exhibited in 1% carbon disulphide solution by the undoubted 3→6β-γ-lactonic methyl ester (III; R = Me). The peaks at 1780 cm.$^{-1}$ indicate a γ-lactonic structure, whilst the absorption bands at 1162 and 1145 cm.$^{-1}$ are probably associated with the carbon–oxygen linkages of the two γ-lactonic methyl esters. Since it is believed that the stretching frequency of the C–O linkage of an equatorial hydroxyl group is greater than that of a corresponding axial hydroxyl group,[6] the bands observed at 1162 and 1145 cm.$^{-1}$ confirm the 6α- and the 6β-configuration assigned to the compounds (I) and (III) respectively.

It thus appears that the slightly strained structure (I) containing ring B as a chair form possesses greater thermodynamic stability than the strainless structure (IV) containing ring B as a boat form (Fig. 3).

Experimental

For general experimental directions, see preceding paper. $[\alpha]_D$ are in $CHCl_3$ unless otherwise stated. Ultraviolet absorption spectra were determined in EtOH on a Unicam SP 500 spectrometer with corrected scale, and infrared absorption spectra in CS_2 on a Perkin-Elmer double-beam instrument.

Sodium Borohydride Reduction of Dimethyl 6-Oxo-2 : 3-secocholestane-2 : 3-dioate (IX; R = Me).—A solution of sodium borohydride (30 mg.) in methanol was added to dimethyl 6-oxo-2 : 3-*seco*cholestane-2 : 3-dioate (120 mg.) in ether–methanol. The mixture was left at 15° for 2 hr., diluted, and extracted with ether. Working up in the usual manner afforded an oil (115 mg.) which was chromatographed on highly active neutralised aluminium oxide (4 g.) prepared in pentane. Elution with pentane to benzene–pentane (3 : 2) gave an oil (12 mg.). Further elution with benzene and benzene–ether (4 : 1) gave methyl 6β-hydroxy-2 : 3-*seco*-cholestane-2 : 3-dioate 3→6β-lactone (III; R = Me) (92 mg.), m. p. 99°, $[\alpha]_D$ +58°.

Treatment of the 3→6α- and 3→6β-Lactonic Acids (I, III; R = H) *with Diazoethane.*—To a solution of 6α-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioic acid 3→6α-lactone (35 mg.) in ether was added excess of ethereal diazoethane. The solution was kept at 0° for 15 min. and the excess of diazoethane then destroyed by addition of 2N-hydrochloric acid. Working up in the usual way afforded an oily ethyl ester (36 mg.).

[5] Windaus, *Ber.*, 1903, **36**, 3752.
[6] Page, *J.*, 1955, 2017.

6β-Hydroxy-2 : 3-*seco*cholestane-2 : 3-dioic acid 3→6β-lactone (35 mg.) by similar treatment also furnished an oily ethyl ester (35 mg.).

The same treatment of cholest-5-ene-3β-carboxylic acid (30 mg.) gave ethyl cholest-5-ene-3β-carboxylate, m. p. 83°.

Methyl Hydrogen 6α-*Hydroxy*-2 : 3-seco*cholestane*-2 : 3-*dioate* (VII).—To a solution of methyl 6α-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioate 3→6α-lactone (I; R = Me) (300 mg.) in dioxan (15 c.c.) was added 0·1N-sodium hydroxide (6·9 c.c.), and the mixture left at 60° for 5 min. The solution was cooled in ice and acidified with 2N-hydrochloric acid; extraction with ether, washing to neutrality with water, and evaporation gave *methyl hydrogen* 6α-*hydroxy*-2 : 3-seco-*cholestane*-2 : 3-*dioate* (VII) (302 mg.), m. p. 167—169°, $[\alpha]_D$ +12° (*c*, 0·8), after crystallisation from methanol [Found (after drying at 60°/0·01 mm. for 6 hr.): C, 72·8; H, 10·2. $C_{28}H_{48}O_5$ requires C, 72·4; H, 10·4%]. The infrared absorption spectrum of a Nujol mull showed bands at 1700, 1680, and 2600 cm.$^{-1}$ (CO_2H), 1735 and 1252 cm.$^{-1}$ (CO_2Me), and at 3260 cm.$^{-1}$ (bonded OH).

Methyl hydrogen 6α-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioate (25 mg.) was refluxed in ethanolic 10% potassium hydroxide (5 c.c.) for 1 hr. The solution was diluted, acidified, and extracted with ether. The ether extract was washed to neutrality with water, dried, and evaporated. The residue by crystallisation from methanol gave 6α-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioic acid 3→6α-lactone (I; R = H) (20 mg.), m. p. and mixed m. p. 200—202°, which with ethereal diazomethane gave methyl 6α-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioate 3→6α-lactone (I; R = Me), m. p. and mixed m. p. 99°.

Methyl Hydrogen 6-*Oxo*-2 : 3-seco*cholestane*-2 : 3-*dioate* (IX; R = H).—Methyl hydrogen 6α-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioate (VII) (230 mg.) was dissolved in acetic acid (35 c.c.), a 2% solution of chromium trioxide in acetic acid (1·9 c.c.) added, and the mixture left at 15° for 16 hr. Excess of chromium trioxide was destroyed by addition of methanol, and the solution diluted; extraction with ether and working up in the usual manner gave *methyl hydrogen* 6-*oxo*-2 : 3-seco*cholestane*-2 : 3-*dioate* (IX; R = H) (220 mg.), m. p. 122—123°, $[\alpha]_D$ +33° (*c*, 0·92), after crystallisation from pentane [Found (after drying at 60°/0·01 mm. for 6 hr.): C, 72·6; H, 10·1. $C_{28}H_{46}O_5$ requires C, 72·7; H, 10·0%].

Treatment of the 6-oxo-half-ester (20 mg.) with ethereal diazomethane and working up in the usual manner gave dimethyl 6-oxo-2 : 3-*seco*cholestane-2 : 3-dioate[5] (IX; R = Me) (21 mg.), m. p. and mixed m. p. 113—114° after crystallisation from acetone–methanol.

3-*Ethyl* 2-*Methyl* 6-*Oxo*-2 : 3-seco*cholestane*-2 : 3-*dioate* (IX; R = Et).—Methyl hydrogen 6-oxo-2 : 3-*seco*cholestane-2 : 3-dioate (IX; R = H) (100 mg.) in ether (10 c.c.) was treated with excess of ethereal diazoethane and left at 0° for 30 min. Excess of diazoethane was destroyed with dilute hydrochloric acid and the ethereal solution worked up in the usual manner to give 3-*ethyl* 2-*methyl* 6-*oxo*-2 : 3-seco*cholestane*-2 : 3-*dioate* (IX; R = Et) (105 mg.), m. p. 77—78°, $[\alpha]_D$ +22·5° (*c*, 0·67), after crystallisation from methanol [Found (after drying at 50°/0·01 mm. for 16 hr.): C, 72·8; H, 10·2. $C_{30}H_{50}O_5$ requires C, 73·4; H, 10·3%].

Sodium Borohydride Reduction of 3-*Ethyl* 2-*Methyl* 6-*Oxo*-2 : 3-seco*cholestane*-2 : 3-*dioate* (IX; R = Et).—Sodium borohydride (20 mg.), dissolved in methanol, was added to a solution of 3-ethyl 2-methyl 6-oxo-2 : 3-*seco*cholestane-2 : 3-dioate (80 mg.) in ether–methanol. The mixture was left at 15° for 2 hr., diluted, and extracted with ether. Working up in the usual manner afforded an oil (81 mg.), which was chromatographed on neutralised aluminium oxide (3 g.) prepared in pentane. Elution with pentane and benzene–pentane (3 : 7) yielded an oil (13 mg.). Elution with benzene–pentane (1 : 1; 3 × 10 c.c.) (7 : 3; 2 × 10 c.c.) gave material (59 mg.) which by crystallisation from pentane gave methyl 6β-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioate 3→6β-lactone, m. p. and mixed m. p. 99°, as the sole crystalline product.

3-p-*Bromophenacyl* 2-*Methyl* 6-*Oxo*-2 : 3-seco*cholestane*-2 : 3-*dioate* (IX; R = *p*-$C_6H_4Br{\cdot}CO{\cdot}CH_2$).—A solution of methyl hydrogen 6-oxo-2 : 3-*seco*cholestane-2 : 3-dioate (IX; R = H) (126 mg.) in 0·1N-sodium hydroxide (2·9 c.c.) was made faintly acid (pH ~6·4) by addition of a few drops of 0·05N-hydrochloric acid. A solution of *p*-bromophenacyl bromide (75 mg.) in ethanol (8 c.c.) was added and the whole refluxed for 1 hr. Crystalline material (103 mg.) separated on cooling at 0° for 16 hr., which by recrystallisation from methanol gave 3-p-*bromophenacyl* 2-*methyl* 6-*oxo*-2 : 3-seco*cholestane*-2 : 3-*dioate* (IX; R = p-$C_6H_4Br{\cdot}CO{\cdot}CH_2$) as plates, m. p. 128—130°, $[\alpha]_D$ +12° (*c*, 0·96), $\lambda_{max.}$ 214 (log ε 3·91) and 258 mμ (log ε 4·06) [Found (after drying at 20°/0·01 mm. for 10 hr.): C, 65·65; H, 7·65. $C_{36}H_{51}O_6Br$ requires C, 65·55; H, 7·8%].

Reduction of 3-p-*Bromophenacyl* 2 *Methyl* 6-*Oxo*-2 : 3-seco*cholestane*-2 : 3-*dioate* (IX; R = *p*-$C_6H_4Br{\cdot}CO{\cdot}CH_2$).—Sodium borohydride (30 mg.), dissolved in methanol, was added to a solution

of the 3-*p*-bromophenacyl 2-methyl ester (82 mg.) in ether–methanol. The mixture was left at 15° for 2 hr., diluted, and extracted with ether. Working up in the usual manner afforded an oil (75 mg.), which by trituration with pentane gave a sticky solid; the pentane was decanted off and the residual solid washed several times with pentane to give crystalline material (20 mg.). Recrystallisation from methanol gave 1-p-*bromophenylethane*-1 : 2-*diol*, m. p. 100—101°, $\lambda_{max.}$ 220 (log ε 4·03) and 265 mμ (log ε 2·6) [Found (after drying at 20°/0·01 mm. for 12 hr.) : C, 44·15; H, 4·35. $C_8H_9O_2Br$ requires C, 44·25; H, 4·2%]. The pentane washings were collected and chromatographed on neutralised aluminium oxide (3 g.) prepared in pentane. Elution with pentane and benzene–pentane (1 : 4; 2 × 8 c.c.) gave an oil (5 mg.). Elution with benzene–pentane (1 : 3; 2 × 8 c.c.)—(1 : 1; 2 × 8 c.c.) gave an oil (38 mg.) (negative Beilstein reaction), which by crystallisation from pentane afforded methyl 6β-hydroxy-2 : 3-*seco*cholestane-2 : 3-dioate 3→6β-lactone, m. p. and mixed m. p. 99°, $[\alpha]_D$ +57°, as the sole crystalline product.

One of us (D. R. J.) acknowledges a grant from the D.S.I.R.; we thank Glaxo Laboratories Ltd. for a gift of cholesterol and for measuring the infrared absorption spectra.

UNIVERSITY OF WALES, UNIVERSITY COLLEGE, SWANSEA. [*Received, September 16th*, 1955.]

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219. *Steroids and Walden Inversion. Part XXIX.* The Configurations of the Bromination Products of 7-Oxocholestan-3β-yl Acetate.*

By D. R. JAMES and C. W. SHOPPEE.

Configurations have been assigned by chemical methods to the epimeric 6-bromo-derivatives of 7-oxocholestan-3β-yl acetate described by Barr, Heilbron, Jones, and Spring;[1] these are consistent with those predicted by Corey[2] and those derived[3] from infrared and ultraviolet spectroscopic evidence.

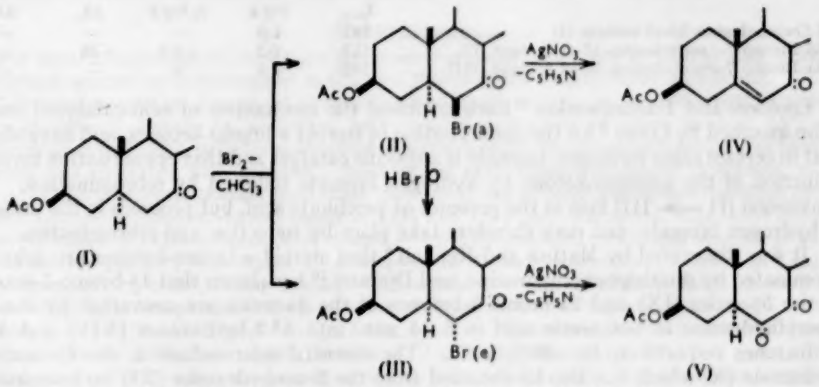
BARR, HEILBRON, E. R. H. JONES, and SPRING[1] found that 7-oxocholestan-3β-yl acetate (I) is not brominated in acetic acid at 35°, but in chloroform at 20° yields two monobromo-derivatives, m. p. 175—176°, $[\alpha]_D$ +35°, and m. p. 142°, $[\alpha]_D$ −9°, the former being convertible into the latter by treatment with hydrogen bromide in acetic acid at 100° for 15 min. The compounds were shown to be epimeric 6-bromo-ketones by their conversion with boiling pyridine (6—8 hr.) into 7-oxocholest-5-en-3β-yl acetate (IV). The 5-bromo-ketone, m. p. 175°, has also been obtained by Tsuda and Hayatsu[4] from (I) by bromination with *N*-bromosuccinimide in carbon tetrachloride at 77° in presence of benzoyl peroxide. On the basis of the dehydrobromination of the bromo-ketone, m. p. 175°, with silver nitrate in boiling pyridine to 7-oxocholest-5-en-3β-yl acetate (IV), and of the transformation of the bromo-ketone, m. p. 142°, by the same reagent into 6 : 7-dioxocholestan-3β-yl acetate (V), Barr, Heilbron, Jones, and Spring[1] assigned the α-configuration to the bromine atom of the epimeride of m. p. 175°, and the β-configuration to the bromine atom of the epimeride of m. p. 142°, erroneously attributing the reluctance of the latter to undergo dehydrobromination to a *trans*-orientation of the atoms involved. These assignments of configuration have been reversed by Fieser and Fieser,[5] and we now prove this reversal to be justified.

Conversion of cholest-6-en-3β-yl acetate (VI) by monoperphthalic acid into the 6α : 7α-epoxide (VII) and cleavage of this with hydrogen bromide in acetic acid has been shown by James, Rees, and Shoppee[6] to furnish 6β-bromo-7α-hydroxycholestan-3β-yl acetate [VIII (6β-Br/7α-OH : diaxial)], from which the 6α : 7α-epoxide (VII) may be regenerated by treatment with potassium hydroxide and subsequent acetylation. Oxidation of

* Part XXVIII, preceding paper.

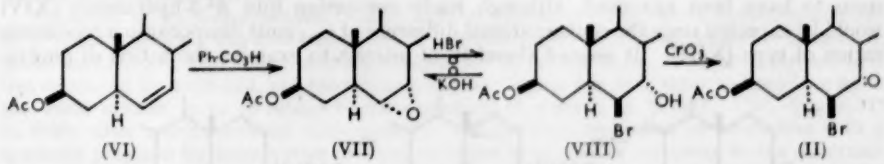
[1] Barr, Heilbron, E. R. H. Jones, and Spring, *J.*, 1938, 334.
[2] Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175.
[3] Cookson, *J.*, 1954, 282.
[4] Tsuda and Hayatsu, *J. Amer. Chem. Soc.*, 1955, **77**, 665.
[5] Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold, New York, 1949, p. 268.
[6] James, Rees, and Shoppee, *J.*, 1955, 1370.

6β-bromo-7α-hydroxycholestan-3β-yl acetate (VIII) with chromium trioxide in acetic acid at 15° gives 6β-bromo-7-oxocholestan-3β-yl acetate (II), m. p. 175—176°, $[\alpha]_D$ +31°,



(II); M. p. 175°, $[\alpha]_D$ +35°. (III); M. p. 142°, $[\alpha]_D$ −9°.

exhibiting an infrared spectrum identical with that of a specimen prepared by bromination of 7-oxocholestan-3β-yl acetate (I). It follows that the epimeride, m. p. 142°, $[\alpha]_D$ −9°, is by exclusion 6α-bromo-7-oxocholestan-3β-yl acetate (III).



Corey [2] has developed methods for predicting the configuration of the bromine atom in α-bromoketo-steroids whose stereochemistry is subject to either thermodynamic or kinetic control. In the case of 7-oxocholestan-3β-yl acetate (I), the predicted configuration of the bromination product under kinetic control is the 6β-bromo-ketone (II), whilst that of the product of thermodynamic control is the 6α-bromo-ketone (III).

R. N. Jones *et al.*[7] have shown that the coplanar arrangement of an equatorial C–Br bond and an adjacent C=O bond leads to an increase (Δ) of 15—20 cm.$^{-1}$ in the frequency of the infrared carbonyl band; but that the mutually perpendicular arrangement of an axial C–Br bond and an adjacent C=O bond has little effect. The infrared absorption spectra of the ketone (I) and the epimeric 6-bromo-ketones (II and III) were determined by Dr. Page, using specimens prepared by Professor D. H. R. Barton and Dr. C. H. Robinson, some years ago, and we are most grateful to Dr. Page and Professor Barton for permission to record the following annexed figures which support the configurations assigned above.

	CO : $\nu_{max.}$ (cm.$^{-1}$)(in CS_2)	Δ	Configuration of $C_{(6)}$–Br bond
7-Oxocholestan-3β-yl acetate (I)	1713	—	—
6β-Bromo-7-oxocholestan-3β-yl acetate (II)	1714	1	Axial
6α-Bromo-7-oxocholestan-3β-yl acetate (III)	1734	21	Equatorial

Cookson [3] has shown that the shift of the wavelength of the ultraviolet absorption maximum of a ketone produced by α-halogen substitution is a function of the angle between the C–Hal and the C=O bond. The change in the position and intensity (Δλ, Δ log ε) of $\lambda_{max.}$ produced by introduction of an axial α-bromine atom is pronounced (Δλ_a *ca.* +28 mμ, Δ log ε *ca.* +0·6), whilst that produced by introduction of an equatorial α-bromine atom is

[7] R. N. Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.

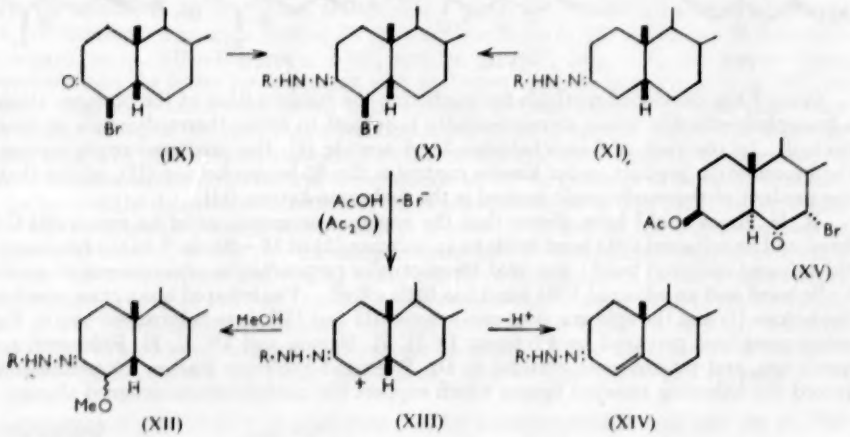
small ($\Delta\lambda_e$ *ca.* −5 mμ, Δ log ε *ca.* 0—+0·3). The annexed figures derived from the measurements recorded by Barr *et al.*[1] confirm the configurations assigned above.

	$\lambda_{max.}$	log ε	Δ log ε	$\Delta\lambda_e$	$\Delta\lambda_a$
7-Oxocholestan-3β-yl acetate (I)	287	1·6	—	—	—
6β-Bromo-7-oxocholestan-3β-yl acetate (II)	313	2·2	+0·6	+26	—
6α-Bromo-7-oxocholestan-3β-yl acetate (III)	282	1·6	0	—	−5

Cookson and Dandegaonker [8] have criticised the mechanism of acid-catalysed enolisation assumed by Corey [2] for the epimerisation of steroid α-bromo-ketones, and have shown that in certain cases hydrogen bromide is a specific catalyst and that epimerisation involves reduction of the α-bromo-ketone by hydrogen bromide followed by rebromination. The conversion (II ⟶ III) fails in the presence of perchloric acid, but proceeds in the presence of hydrogen bromide, and may therefore take place by reduction and rebromination.

It was discovered by Mattox and Kendall [9] that steroid α-bromo-ketones are dehydrobrominated by dinitrophenylhydrazine, and Djerassi [10] has shown that 4β-bromo-3-ketones of the 5β-series (IX) and 2α-bromo-3-ketones of the 5α-series are converted by dinitrophenylhydrazine in hot acetic acid in 3—5 min. into Δ^4-3-hydrazones (XIV) and Δ^1-3-hydrazones respectively in ~90% yield. The essential intermediate is the 4β-bromo-3-hydrazone (X) which can also be obtained from the 3-oxohydrazone (XI) by bromination in chloroform, and the mechanism proposed by Mattox and Kendall [11] involves a mesomeric cation represented by (XIII), which may unite with an external anion, *e.g.*, in methanol to give the 4ξ-methoxy-3-hydrazone (XII), or expel a proton to yield the Δ^4-3-hydrazone (XIV).

4α-Bromo-3-ketones of the 5α-series are not readily accessible, and therefore do not seem to have been examined, although ready conversion into Δ^4-3-hydrazones (XIV) would be expected since the configurational difference at $C_{(4)}$ must disappear in a mesomeric cation of type (XIII). It seemed therefore of interest to examine the action of dinitro-



phenylhydrazine on the 6-bromo-7-ketones (II and III). Unexpectedly, both 6-bromo-7-ketones were recovered unchanged after treatment with dinitrophenylhydrazine in hot acetic acid or in ethanol–sulphuric acid. The rate-determining step in hydrazone formation is nucleophilic attack at the carbonyl-carbon atom, and normally this proceeds without difficulty at $C_{(7)}$ since cholestan-7-one readily affords a dinitrophenylhydrazone; [12]

[8] Cookson and Dandegaonker, *J.*, 1955, 352.
[9] Mattox and Kendall, *J. Amer. Chem. Soc.*, 1948, **70**, 882.
[10] Djerassi, *ibid.*, 1949, **71**, 1003.
[11] Mattox and Kendall, *ibid.*, 1950, **72**, 2290; cf. McGuckin and Kendall, *ibid.*, 1952, **74**, 5811.
[12] Cremlyn and Shoppee, *J.*, 1954, 3575.

similarly, although cholestan-6-one readily forms a dinitrophenylhydrazone,[13] 7α-bromo-6-oxocholestan-3β-yl acetate (XV) fails to do so. Differences in the reactivities of α-bromo-2 : 4-dinitrophenylhydrazones have been encountered by Ramirez and Kirby.[14]

Experimental

For general experimental directions see preceding paper. $[\alpha]_D$ are in $CHCl_3$, and infrared absorption spectra were determined in CS_2 in a Perkin-Elmer double-beam instrument.

7-Oxocholestan-3β-yl Acetate.—7-Oxocholest-5-en-3β-yl acetate, m. p. 156—158°, obtained from cholesteryl acetate by oxidation with chromium trioxide in acetic acid at 55°, was hydrogenated with 20% palladium–charcoal in acetic acid;[15] the resulting solution was filtered, diluted, and extracted with pentane. Working up gave 7-oxocholestan-3β-yl acetate, m. p. 141—142°, after recrystallisation from ether–methanol; the infrared absorption spectrum in 1% carbon disulphide solution showed bands at 1737 and 1236 cm.$^{-1}$ (OAc) and 1713 cm.$^{-1}$ (CO).

Bromination of 7-Oxocholestan-3β-yl Acetate.—A freshly prepared solution of bromine (0·84 g.) in chloroform (15 c.c.) was added to a solution of 7-oxocholestan-3β-yl acetate (2·2 g.) in chloroform (15 c.c.) at 20°, during 15 min. Chloroform was removed under reduced pressure and the residual solid recrystallised from acetone, to give 6β-bromo-7-oxocholestan-3β-yl acetate (550 mg.), m. p. 175—176°, $[\alpha]_D$ +37° (*c*, 1·12), which in 1% carbon disulphide solution showed bands at 1738 and 1234 cm.$^{-1}$ (OAc) and 1714 cm.$^{-1}$ (CO, adjacent to axial Br).

The acetone mother-liquor was evaporated and the residual solid (1·5 g.) chromatographed in pentane on aluminium oxide (50 g.). Elution with pentane and benzene–pentane (1 : 9; 3 × 150 c.c.) gave material which could not be crystallised, but elution with benzene–pentane (1 : 2; 2 × 150 c.c.) afforded 6α-bromo-7-oxocholestan-3β-yl acetate (350 mg.), m. p. 141—142°, $[\alpha]_D$ −10·5° (*c*, 1·41), after crystallisation from aqueous acetic acid. The infrared spectrum in 1% carbon disulphide solution showed bands at 1738 and 1234 cm.$^{-1}$ (OAc) and 1734 cm.$^{-1}$ (CO, adjacent to equatorial Br).

Oxidation of 6β-Bromo-7α-hydroxycholestan-3β-yl Acetate.—6β-Bromo-7α-hydroxycholestan-3β-yl acetate (50 mg.) was dissolved in acetic acid (10 c.c.), a solution of chromium trioxide in acetic acid (1 c.c.; 2%) added, and the solution left at 15° for 16 hr. Excess of chromic acid was destroyed by methanol, and the solution diluted; extraction with ether and working up in the usual manner gave 6β-bromo-7-oxocholestan-3β-yl acetate, m. p. 175—176°, $[\alpha]_D$ +31° (*c*, 0·66), after recrystallisation from acetone; this gave no depression on admixture with a specimen prepared by bromination of 7-oxocholestan-3β-yl acetate according to the directions of Barr *et al.*[1] The infrared absorption in 1% carbon disulphide solution showed bands at 1738 and 1234 cm.$^{-1}$ (OAc) and 1714 cm.$^{-1}$ (CO, adjacent to axial Br), and was identical with that of a genuine specimen.

Treatment with Dinitrophenylhydrazine.—(*a*) The 6β-bromo-7-ketone (II) (72 mg.) was dissolved in acetic acid (5 c.c.; saturated with nitrogen) in an atmosphere of nitrogen. Dinitrophenylhydrazine (30 mg., 1·1 mols.) was added and the solution heated at ~120° for 5 min. On cooling, no precipitate was formed, but needles of the starting material separated gradually; dilution and filtration gave unchanged 6β-bromo-7-ketone, m. p. 174—176°, mixed m. p. 175°. In a second experiment, the 6β-bromo-7-ketone, similarly dissolved in ethanol, was heated to boiling with a solution of 2 : 4-dinitrophenylhydrazine in a few drops of concentrated sulphuric acid and ethanol; no hydrazone separated on cooling.

(*b*) The 6α-bromo-7-ketone (III) (70 mg.), dissolved in acetic acid (4 c.c.), was treated with 2 : 4-dinitrophenylhydrazine (30 mg., 1·1 mols.) at 120° for 5 min. as under (*a*). No precipitate was formed on cooling, and dilution and filtration yielded the unchanged 6α-bromo-7-ketone, m. p. 140°, mixed m. p. 140—142°.

(*c*) The 7α-bromo-6-ketone (XV) (112 mg.) was heated with 2 : 4-dinitrophenylhydrazine (47 mg., 1·1 mols.) in acetic acid (5 c.c.) at 100° for 5 min. as under (*a*). No precipitate was formed, and after 16 hr. only a little of the unchanged 7α-bromo-6-ketone, m. p. and mixed m. p. 144—145°, had separated.

One of us (D. R. J.) gratefully acknowledges the support of the Department of Scientific and Industrial Research; we thank Glaxo Laboratories Ltd. for gifts of cholesterol and for determination of infrared spectra.

University of Wales, University College, Swansea. [*Received, October 6th*, 1955.]

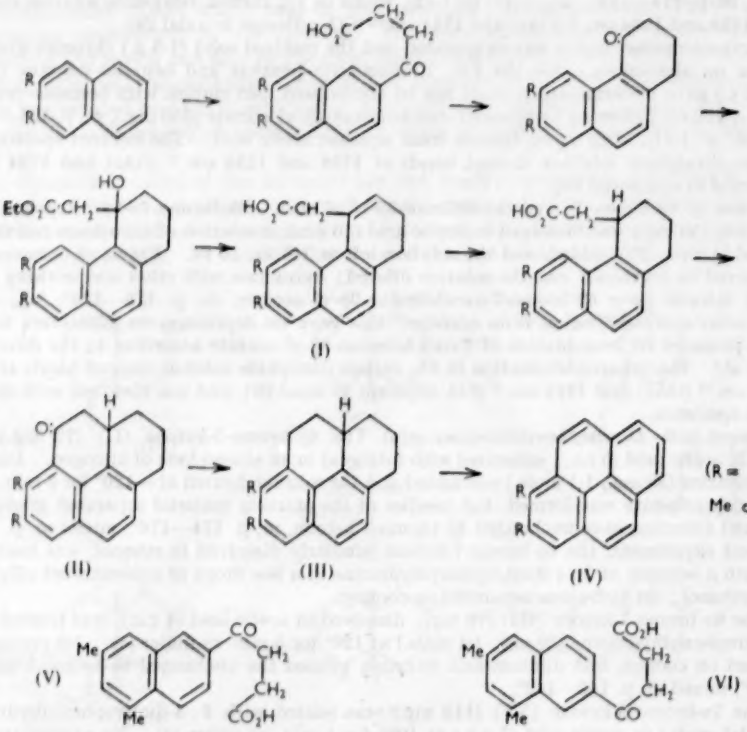
[13] Jenkins, Shoppee, and Summers, to be published.
[14] Ramirez and Kirby, *J. Amer. Chem. Soc.*, 1952, **74**, 4331; 1953, **75**, 6026.
[15] Windaus and Kirchner, *Ber.*, 1920, **53**, 614.

220. *Syntheses of Hydrocarbons possibly related to Carcinogenic Factors in City Smoke.*

By G. R. Clemo and N. D. Ghatge.

3 : 4-Dimethyl- and 3 : 4-diethyl-pyrene and 7 : 9-dimethylaceanthrene have been synthesised from disubstituted naphthalenes.

One of us [1] described the isolation, from a fraction of city smoke, of a hydrocarbon X since shown [2] to be carcinogenic to mice. Its analysis, ultraviolet spectrum, and other properties resembled those of a substituted pyrene, so it was decided to synthesise certain alkylpyrenes for comparison. Since in the benzanthracene series two methyl groups in a terminal ring accentuate the carcinogenic activity and since 3 : 4-benzopyrene is a well-known carcinogen, the first syntheses were those of the hitherto undescribed 3 : 4-dimethyl- and 3 : 4-diethyl-pyrene.



The synthetical route shown in the annexed scheme was explored by Bograchove [3] as far as (II; R = Me) but the acid then formulated as (I) melts 23° lower than our acid. This difference could clearly be due to a different position of the double bond. Clemmensen reduction of the ketone (II; R = Me) has now given the hexahydrodimethylpyrene (III; R = Me) which on dehydrogenation by palladium–charcoal gave 3 : 4-dimethylpyrene

[1] Clemo, Presidential Address, British Assoc., Sect. B, 1953.
[2] Clemo and Miller, *Chem. and Ind.*, 1955, 38.
[3] Bograchove, *J. Amer. Chem. Soc.*, 1944, **66**, 1613.

(IV; R = Me). Similarly, by starting from 2 : 3-diethylnaphthalene, 3 : 4-diethylpyrene was obtained. Neither compound however corresponds to the hydrocarbon X : the ultraviolet spectra of the three compounds are given in Fig. 1.

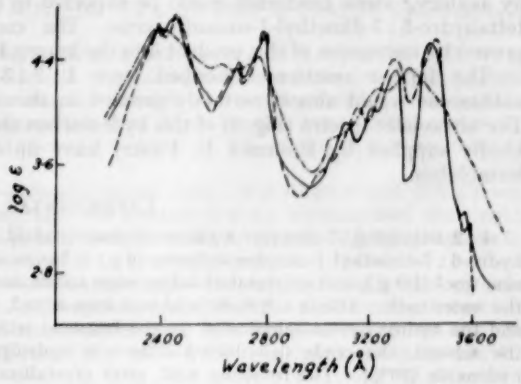


FIG. 1. *Absorption spectra of* (——) *3 : 4-dimethylpyrene,* (– – –) *3 : 4-diethylpyrene, and* (— · —) *substance X in ethyl alcohol.*

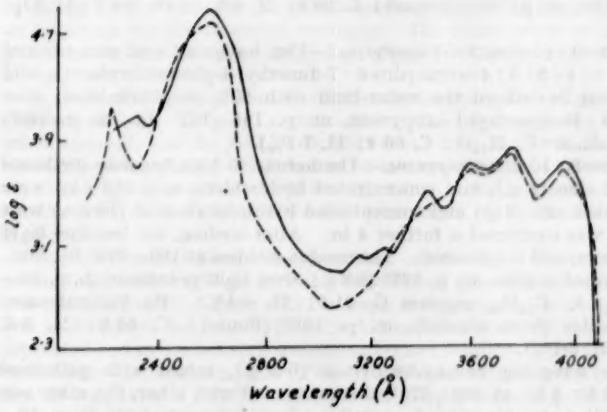
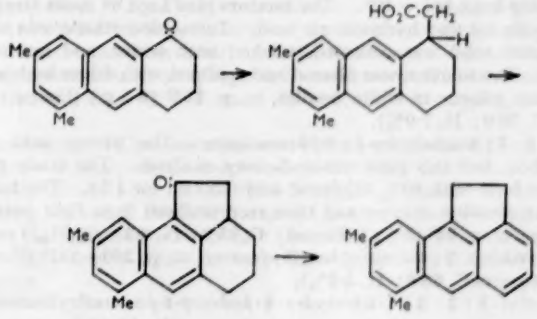


FIG. 2. *Absorption spectra of* (——) *7 : 9- and* (– – –) *7 : 8-dimethylaceanthrene in ethyl alcohol.*

Continuing, we attempted to prepare other dialkylated pyrenes, such as 3 : 5-dimethylpyrene. Succinoylation of 1 : 3-dimethylnaphthalene in a β-position could give either keto-acid (V) or (VI) or a mixture, but only one pure acid was actually obtained. If this were (V), it should lead, by the reactions described above for 3 : 4-dimethylpyrene, to



the 3 : 5-dimethyl analogue. The ultraviolet spectrum (Fig. 2) of the compound obtained is, however, different from that of authentic pyrenes, pointing to our acid's being (VI); on Clemmensen reduction this would give β-(6 : 8-dimethyl-2-naphthyl)butyric acid and, by analogy,[4] steric hindrance would be expected to lead to its cyclisation to 1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethyl-1-oxoanthracene. The correctness of this view has been proved by conversion of this product into the known 1 : 3-dimethylanthracene.

The further reactions described from 1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethyl-1-oxoanthracene would almost certainly proceed as shown, giving 7 : 9-dimethylaceanthrene. The ultraviolet spectra (Fig. 2) of this hydrocarbon and of 7 : 8-dimethylaceanthrene (very kindly supplied by Professor L. Fieser) leave no doubt as to the correctness of the formulation.

Experimental

1 : 2-Dihydro-6 : 7-dimethyl-4-phenanthrylacetic Acid.—To a solution of 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethyl-1-oxophenanthrene (6 g.) in benzene (25 c.c.), ethyl bromoacetate (5·4 c.c.), zinc wool (1·9 g.), and a crystal of iodine were added and the mixture was warmed for 4 hr. on the water-bath. Dilute sulphuric acid was then added, the benzene layer separated and dried, and the hydroxy-ester dehydrated (in the benzene) with phosphoric oxide. After removal of the solvent, the crude dehydrated ester was hydrolysed by refluxing ethanolic potassium hydroxide (20%). The resulting acid, after crystallisation from acetic acid (charcoal), gave colourless needles, m. p. 209° (lit., m. p. 186°) (Found: C, 80·9; H, 6·8. Calc. for $C_{18}H_{18}O_2$: C, 81·2; H, 6·8%).

1 : 2 : 2a : 3 : 4 : 5-Hexahydro-9 : 10-dimethyl-1-oxopyrene.—The foregoing acid was reduced catalytically (platinum oxide) to 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethyl-4-phenanthrylacetic acid (m. p. 167—168°) which, when heated on the water-bath with 80% sulphuric acid, gave 1 : 2 : 2a : 3 : 4 : 5-hexahydro-9 : 10-dimethyl-1-oxopyrene, m. p. 161—162° (lit., m. p. 160°) (Found: C, 86·7; H, 7·5. Calc. for $C_{18}H_{18}O$: C, 86·4; H, 7·2%).

1 : 2 : 2a : 3 : 4 : 5-Hexahydro-9 : 10-dimethylpyrene.—The ketone (0·5 g.), benzene–methanol (20 c.c.; 1 : 1), amalgamated zinc (2 g.), and concentrated hydrochloric acid (10 c.c.) were refluxed for 4 hr. Amalgamated zinc (2 g.) and concentrated hydrochloric acid (10 c.c.) were then added and the refluxing was continued a further 4 hr. After cooling, the benzene layer was separated, washed with water, and evaporated. The residue distilled at 190—200°/0·1 mm., giving a *hydrocarbon* which formed needles, m. p. 127° (0·3 g.), from light petroleum (b. p. 40—60°) (Found: C, 91·4; H, 8·8. $C_{18}H_{20}$ requires C, 91·5; H, 8·5%). Its *trinitrobenzene derivative* formed orange needles (from alcohol), m. p. 163° (Found: C, 64·5; H, 5·5. $C_{24}H_{23}O_6N_3$ requires C, 64·2; H, 5·1%).

3 : 4-Dimethylpyrene.—The foregoing hexahydro-pyrene (0·2 g.), mixed with palladised charcoal (10 mg.), was heated for ½ hr. at 260—270°, then extracted with ether, the ether was removed, and the *product* distilled at 0·1 mm. and crystallised from light petroleum (b. p. 40—60°), giving needles, m. p. 103° (Found: C, 93·7; H, 6·0. $C_{18}H_{14}$ requires C, 93·9; H, 6·1%). Its *trinitrobenzene derivative* formed orange needles (from alcohol), m. p. 217—218° (Found: C, 65·0; H, 4·3. $C_{24}H_{17}O_6N_3$ requires C, 65·0; H, 3·8%).

β-(6 : 7-Diethyl-2-naphthoyl)propionic Acid.—To 2 : 3-diethylnaphthalene (10 g.) and succinic anhydride (5·4 g.) in tetrachloroethane (75 c.c.), powdered aluminium chloride (16 g.) was added, the temperature being kept below 35°. The mixture was kept at room temperature for 6 hr., then decomposed with ice and hydrochloric acid. Tetrachloroethane was removed in steam. The resulting greenish solid was collected, washed with water, and extracted with sodium carbonate solution. The solution was filtered and acidified with dilute hydrochloric acid. The *acid* crystallised from toluene in white needles, m. p. 155° (8·5 g.) (Found: C, 76·0; H, 7·3. $C_{18}H_{20}O_3$ requires C, 76·0; H, 7·0%).

6 : 7-Diethyl-1 : 2 : 3 : 4-tetrahydro-4-oxophenanthrene.—The above acid was reduced by Clemmensen's method, but this gave unsatisfactory analyses. The crude product (5 g.) was heated on the water-bath with 80% sulphuric acid (25 c.c.) for 1 hr. The *ketone* thus obtained was passed down an alumina column and then recrystallised from light petroleum (b. p. 40—60°), forming needles, m. p. 64° (3·6 g.) (Found: C, 85·9; H, 8·3. $C_{18}H_{20}O$ requires C, 85·7; H, 7·9%). It gave a reddish 2 : 4-*dinitrophenylhydrazone*, m. p. 236—237° (Found: C, 66·2; H, 5·5. $C_{24}H_{24}O_4N_4$ requires C, 66·6; H, 5·5%).

Ethyl 6 : 7-Diethyl-1 : 2 : 3 : 4-tetrahydro-4-hydroxy-4-phenanthrylacetate.—The foregoing

[4] Haworth, *J.*, 1934, 1950.

ketone (3 g.) in benzene (25 c.c.) was treated with ethyl bromoacetate (2·9 c.c.), zinc wool (0·85 g.), and a crystal of iodine. The mixture was warmed on the water-bath for 4 hr., dilute sulphuric acid added, the benzene layer separated and dried (Na_2SO_4), and the benzene removed. The residual ester, when kept in light petroleum (b. p. 40—60°) at 0°, afforded needles which, recrystallised from this solvent, melted at 72—73° (1·2 g.) (Found : C, 77·4; H, 8·5. $C_{22}H_{26}O_3$ requires C, 77·6; H, 8·2%).

6 : 7-*Diethyl*-1 : 2-*dihydro*-4-*phenanthrylacetic Acid.*—A solution of 6 : 7-diethyl-1 : 2 : 3 : 4-tetrahydro-4-hydroxy-4-phenanthrylacetic acid (1 g.) and phosphoric oxide (0·5 g.) in benzene (20 c.c.) was refluxed for 1·5 hr. The crude unsaturated ester was hydrolysed with alcoholic potassium hydroxide (20%); the resulting *acid*, after crystallisation from alcohol (charcoal), formed needles, m. p. 194—195° (0·6 g.) (Found : C, 81·7; H, 7·7. $C_{20}H_{22}O_2$ requires C, 81·6; H, 7·5%).

6 : 7-*Diethyl*-1 : 2 : 3 : 4-*tetrahydro*-4-*phenanthrylacetic Acid.*—The dihydro-acid (0·6 g.) was catalytically reduced (platinum oxide), and the *product* (0·6 g.) recrystallised from light petroleum (b. p. 40—60°) in needles, m. p. 163° (Found : C, 81·5; H, 8·0. $C_{20}H_{24}O_2$ requires C, 81·1; H, 8·1%).

9 : 10-*Diethyl*-1 : 2 : 2a : 3 : 4 : 5-*hexahydro*-1-*oxopyrene.*—The tetrahydro-acid (0·5 g.) was heated on the water-bath for ½ hr. with 80% sulphuric acid (2·5 c.c.). The resulting *ketone* was passed down a column of alumina and recrystallised from light petroleum (b. p. 40—60°) in yellowish needles, m. p. 105° (0·33 g.) (Found : C, 86·5; H, 8·3. $C_{20}H_{22}O$ requires C, 86·3; H, 7·9%).

9 : 10-*Diethyl*-1 : 2 : 2a : 3 : 4 : 5-*hexahydropyrene.*—The hexahydropyrene (0·3 g.) was reduced as described for the dimethyl analogue. The *hydrocarbon* obtained recrystallised from light petroleum as needles, m. p. 70° (0·2 g.) (Found : C, 91·1; H, 9·4. $C_{20}H_{24}$ requires C, 90·9; H, 9·1%).

3 : 4-*Diethylpyrene.*—The diethylhexahydropyrene (0·1 g.) was heated with palladised charcoal (50 mg.) for ½ hr. at 260—270°. The organic matter was extracted with ether, the ether removed, and the *product* distilled at 0·1 mm. and crystallised from light petroleum (b. p. 40—60°), giving plates, which fluoresced in ultraviolet light and had m. p. 84° (Found : C, 92·6; H, 7·5. $C_{20}H_{18}$ requires C, 93·0; H, 7·0%). Its *trinitrobenzene derivative* formed orange needles (from alcohol), m. p. 173—174° (Found : C, 66·2; H, 4·4. $C_{26}H_{21}O_6N_3$ requires C, 66·2; H, 4·5%).

β-(6 : 8-*Dimethyl*-2-*naphthoyl*)*propionic Acid.*—To 1 : 3-dimethylnaphthalene [5] (10 g.) and succinic anhydride (6·4 g.) in tetrachloroethane (75 c.c.), powdered aluminium chloride (19 g.) was added at <35°. After 6 hr. at room temperature, the complex was decomposed with ice and hydrochloric acid, and the tetrachloroethane removed in steam. The resultant mass was separated and extracted with sodium carbonate solution. The solution was filtered and acidified with dilute hydrochloric acid. The *acid*, filtered off and recrystallised from toluene, had m. p. 184° (9·2 g.) (Found : C, 74·7; H, 6·2. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%).

γ-(6 : 8-*Dimethyl*-2-*naphthyl*)*butyric Acid.*—The foregoing acid (9 g.), toluene (50 c.c.), amalgamated zinc (27 g.), and concentrated hydrochloric acid (50 c.c.) were refluxed for 8 hr., with the addition of further acid (2 × 20 c.c.) at intervals of 3 hr. The toluene layer was separated, washed with water, dried (Na_2SO_4), and distilled. The residual *acid*, recrystallised from light petroleum, had m. p. 146° (5·2 g.) (Found : C, 79·2; H, 7·5. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%).

1 : 2 : 3 : 4-*Tetrahydro*-5 : 7-*dimethyl*-1-*oxoanthracene.*—The preceding butyric acid (7 g.) was heated on the water-bath for 1·5 hr. with 80% sulphuric acid (35 c.c.), then poured on ice. The organic matter was extracted with ether, and the solution washed with a solution of sodium carbonate, then with water, dried (Na_2SO_4), and evaporated. The residual *ketone*, crystallised from light petroleum, had m. p. 110° (Found : C, 85·9; H, 7·4. $C_{16}H_{16}O$ requires C, 85·7; H, 7·2%).

1 : 3-*Dimethylanthracene.* The oxoanthracene (0·2 g.) was reduced by Clemmensen's method to 1 : 2 : 3 : 4-*tetrahydro*-5 : 7-*dimethylanthracene*, b. p. 120—125°/mm., m. p. 35°, which could not be crystallised easily (Found : C, 91·3; H, 8·7. $C_{16}H_{18}$ requires C, 91·4; H, 8·6%). On dehydrogenation with palladised charcoal this gave a product which distilled at 140—145°/2 mm. and solidified. On recrystallisation from light petroleum it melted at 78° (lit., m. p. 78—79°), and gave a reddish picrate, m. p. 132° (lit., m. p. 132—133°). Its ultraviolet spectrum is similar to that of anthracene.

[5] Barnett and Sanders, *J.*, 1933, 434.

3 : 4-*Dihydro*-5 : 7-*dimethyl*-1-*anthrylacetic Acid*.—To a solution of 1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethyl-1-oxoanthracene (4 g.) in benzene (25 c.c.), ethyl bromoacetate (3 c.c.), zinc wool (1·3 g.), and a crystal of iodine were added and the mixture warmed for 4 hr. Dilute sulphuric acid was then added, the benzene layer separated and dried (Na_2SO_4), and the hydroxy-ester dehydrated in the benzene with phosphoric oxide. After removal of the solvent, the crude dehydrated ester was hydrolysed by refluxing ethanolic potassium hydroxide (20%). The resulting *acid* formed needles, m. p. 182° (3 g.), from light petroleum (Found : C, 81·2; H, 6·8. $C_{16}H_{16}O_2$ requires C, 81·2; H, 6·8%).

1 : 2 : 3 : 4-*Tetrahydro*-5 : 7-*dimethyl*-1-*anthrylacetic Acid*.—The dihydro-acid (1 g.) was reduced over platinum oxide in quantitative yield. The *tetrahydro-acid*, crystallised from light petroleum, had m. p. 125° (0·99 g.) (Found : C, 80·2; H, 7·1. $C_{16}H_{20}O_2$ requires C, 80·6; H, 7·4%).

2a : 3 : 4 : 5-*Tetrahydro*-7 : 9-*dimethylaceanthrene*.—Heating the preceding acid (0·7 g.) on the water-bath ½ hr. with 80% sulphuric acid (3·5 c.c.) gave a ketone, which, purified by passage through alumina and crystallisation from light petroleum, had m. p. 116° (0·42 g.) (Found : C, 86·7; H, 7·6. $C_{15}H_{16}O$ requires C, 86·4; H, 7·2%). This 2a : 3 : 4 : 5-*tetrahydro*-7 : 9-*dimethyl*-1-*oxoaceanthrene* (0·4 g.) was reduced by Clemmensen's method, as described for the preparation of the hexahydrodimethylpyrene. The *hydrocarbon* obtained, when crystallised from light petroleum, had m. p. 50° (0·3 g.) (Found : 91·3; H, 8·7. $C_{15}H_{20}$ requires C, 91·5; H, 8·5%). Its *trinitrobenzene derivative* (from alcohol) melted at 165° (Found : C, 64·1; H, 5·3. $C_{24}H_{23}O_6N_3$ requires C, 64·1; H, 5·1%).

7 : 9-*Dimethylaceanthrene*.—The tetrahydroaceanthrene (0·2 g.) was heated with palladised charcoal for ½ hr. at 260—270°. The aromatic *hydrocarbon* then extracted with ether sublimed at 2 mm. and crystallised from alcohol in yellowish needles, m. p. 134° (0·11 g.) (Found : C, 92·8; H, 7·1. $C_{16}H_{16}$ requires C, 93·1; H, 6·9%). It gave a reddish *trinitrobenzene derivative*, m. p. 176° (Found : C, 64·5; H, 4·5. $C_{24}H_{19}O_6N_3$ requires C, 64·7; H, 4·3%).

One of us (N. G. D.) thanks Rajasaheb Kagal for some financial assistance.

King's College, Newcastle upon Tyne, 1. [*Received, August 15th*, 1955.]

221. *The Constitution of an Oat-straw Xylan.*

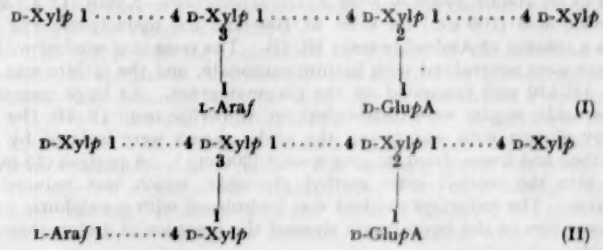
By G. O. Aspinall and K. C. B. Wilkie.

Fractionation of oat-straw hemicellulose yielded a xylan containing small quantities of arabinose (*ca.* 3%) and uronic acid (*ca.* 3·5%) residues. Hydrolysis of the methylated polysaccharide gave 2 : 3 : 5-tri-*O*-methyl-L-arabinose, 2 : 3 : 4-tri-*O*-methyl-D-xylose, 2 : 3-di-*O*-methyl-D-xylose, 2-*O*-methyl-D-xylose, and 3-*O*-methyl-2-*O*-(2 : 3 : 4-tri-*O*-methyl-D-glucuronosyl)-D-xylose in the approximate molar ratios 1 : 1 : 41 : 1 : 1. It is concluded from these and other experiments that the xylan molecule is composed of 40—45 β-D-xylopyranose residues, the main chain carrying two side-chains linked through positions 3 and 2 of the D-xylose residues, and terminated by L-arabofuranose and 4-*O*-methyl-D-glucopyranuronic acid residues respectively. Possible structures for the polysaccharide are discussed.

In continuation of our structural studies of the hemicelluloses of lignified tissues, this paper describes the results of an examination of a xylan from oat straw. The hemicellulose was extracted from the delignified straw with cold aqueous sodium hydroxide, and hydrolysis of the polysaccharide indicated the presence of arabinose (5·6%) in addition to xylose residues. Repeated fractionations of the hemicellulose *via* the copper complex gave a xylan in which the proportion of arabinose residues had been reduced, but no xylan devoid of arabinose residues could be isolated. The xylan, thus obtained, gave on hydrolysis xylose and arabinose in the ratio 32 : 1 and had a uronic anhydride content of 3·5%. The acidic fraction obtained on hydrolysis of the xylan was converted into the methyl ester methyl glycoside, reduction of which with lithium aluminium hydride followed by hydrolysis of the reduction product yielded xylose and 4-*O*-methylglucose together with a trace of glucose. The acidic residues present in the polysaccharide, therefore, were those of glucuronic acid present for the most part as the 4-methyl ether.

The xylan was converted into the methylated derivative and the sugars obtained on hydrolysis of the methylated polysaccharide were partitioned on cellulose. The following sugars, which were isolated and characterised by the formation of crystalline derivatives—2 : 3 : 5-tri-*O*-methyl-L-arabinose, 2 : 3 : 4-tri-*O*-methyl-D-xylose, 2 : 3-di-*O*-methyl-D-xylose and 2-*O*-methyl-D-xylose—were present in the molar ratios 0·8 : 1·0 : 4·1 : 1·2. In addition a tetra-*O*-methylaldobiouronic acid was isolated and shown to be 3-*O*-methyl-2-*O*-(2 : 3 : 4-tri-*O*-methyl-D-glucuronosyl)-D-xylose as reduction of its methyl ester methyl glycoside with lithium aluminium hydride followed by hydrolysis gave 2 : 3 : 4-tri-*O*-methyl-D-glucose and 3-*O*-methyl-D-xylose.

The main structural features of this oat-straw xylan are clear from these results. The isolation of the above aldobiouronic acid shows that each xylan chain contains a single D-glucuronic acid residue (probably as the 4-methyl ether) linked directly to the main chain through position 2 of a D-xylose residue. The isolation of 2 : 3 : 5-tri-*O*-methyl-L-arabinose accounts for all the arabinose residues present in the polysaccharide. The quantity of this compound isolated, together with that of 2-*O*-methyl-D-xylose, indicates that on the average each xylan carries a second side-chain terminated by an L-arabofuranose unit. It is not possible on the present evidence to distinguish between structures in which the L-arabofuranose residue is linked directly to the main chain (I) and those in which a side-chain of D-xylose residues is terminated by an arabinose residue (II), nor is it possible to indicate the relative positions in the main chain of the two branch points. The quantity of monomethylxylose isolated was only slightly in excess of that required by the branching point to the L-arabofuranose residue. The sugar, therefore, was not present in sufficient amount to accommodate a side-chain terminated by a D-xylopyranose residue, and it is probable that the excess arose from undermethylation of the polysaccharide and/or demethylation during hydrolysis. The results of periodate oxidation of the xylan were consistent with the picture of a xylan of 40—45 residues with side-chains terminated by an L-arabofuranose residue and a 4-*O*-methyl-D-glucuronic acid residue, in that 1·0 mole of periodate was consumed per pentose residue and 1 mole of formic acid was released per 15·7 residues, corresponding to a molecule with one non-reducing D-xylopyranose residue per chain of 47 residues.



These results indicate that this xylan is of a similar molecular size to the wheat-straw xylan [1] previously examined in these laboratories. The occurrence of side-chains terminated by L-arabofuranose residues and linked to the main chain through position 3 of the D-xylose residue is a structural feature also found in the hemicelluloses of esparto grass [2] and of wheat-straw.[3–5] On the other hand, the linking of 4-*O*-methyl-D-glucuronic acid residues to position 2 of the xylose residues recalls a linkage characteristic of the wood hemicelluloses [6–8] rather than that of wheat straw.[9] It is of interest that in this investigation it was not possible by the fractionation of oat-straw hemicellulose to isolate a xylan

[1] Aspinall and Mahomed, *J.*, 1954, 1731.
[2] Aspinall, Hirst, Moody, and Percival, *J.*, 1953, 1631.
[3] Adams, *Canad. J. Chem.*, 1952, **30**, 698.
[4] Ehrenthal, Montgomery, and Smith, *J. Amer. Chem. Soc.*, 1954, **76**, 5509.
[5] Roudier, *Compt. rend.*, 1953, **237**, 840.
[6] Jones and Wise, *J.*, 1952, 3389.
[7] Aspinall, Hirst, and Mahomed, *J.*, 1954, 1734.
[8] Gorrod and Jones, *J.*, 1954, 2522.
[9] Bishop, *Canad. J. Chem.*, 1953, **31**, 134.

devoid of arabinose residues, although it is still possible that such xylans may be present in oat straw. This fact, however, confirms the view that the xylans devoid of arabinose residues isolated from esparto grass [10] and wheat straw [1] by similar methods were true xylans and not artefacts from which the relatively labile arabofuranose residues had been removed during their isolation.

It is probable that the xylan studied in this investigation is only one of many xylans present in oat straw. In order, however, to decide whether the xylans from a particular source differ only in molecular size and in the number rather than in the nature of the residues linked as side-chains, or whether different structural features are present in these several xylans, it will be necessary for much more selective methods for the fractionation of such closely related polysaccharides to be developed.

Experimental

Paper partition chromatography was carried out on Whatman No. 1 filter paper with the upper layers of the following solvents system (v/v): (A) butan-1-ol–benzene–pyridine–water (5 : 1 : 3 : 3); (B) butan-1-ol–ethanol–water (5 : 1 : 4); (C) butan-1-ol–acetic acid–water (4 : 1 : 5); and (D) benzene–ethanol–water (167 : 47 : 15).

Isolation and Fractionation of Oat-straw Hemicellulose.—Oat straw (variety Sun II, cut in September 1952; 365 g.) was delignified by Wise's method.[11] The holocellulose (*ca.* 220 g.) was extracted with sodium hydroxide solution (4%), the extract was acidified with glacial acetic acid, and the oat-straw hemicellulose (46 g.) was precipitated by the addition of an equal volume of acetone. The crude hemicellulose had $[\alpha]_D^{18}$ −94·7° (*c* 0·6 in N-sodium hydroxide) and chromatographic examination of the hydrolysate by Hirst and Jones's method [12] in solvent A showed the presence of xylose (94·4%) and arabinose (5·6%) (calc. as 100% pentose). The hemicellulose was fractionated by five successive precipitations of the copper complex formed on addition of Fehling's solution to a solution in sodium hydroxide (4%). The oat-straw xylan (19 g.) thus obtained had $[\alpha]_D^{18}$ −95·0° (*c* 0·5 in N-sodium hydroxide) [Found: ash (as sulphate), 0·8%; lignin, 3·3; uronic anhydride (by decarboxylation), 3·5; OMe, 0·5%] and was used in all subsequent investigations. Chromatographic examination of the hydrolysate showed the presence of xylose (97·0%) and arabinose (3·0%) (calc. as 100% pentose).

Examination of the Acidic Fraction from Xylan Hydrolysis.—Xylan (14 g.) was hydrolysed with 0·5N-sulphuric acid (100 c.c.) for 6 hr. at 100° and the hydrolysate was neutralised by passage through a column of Amberlite resin IR-4B. The resin was washed with 2N-sulphuric acid, the washings were neutralised with barium carbonate, and the filtrate was deionised with Amberlite resin IR-120 and examined on the chromatogram. As large quantities of xylose were present the acidic sugars were re-adsorbed on Amberlite resin IR-4B, the neutral sugars were removed by elution with water, and the acidic sugars were isolated by the procedure previously described and freeze-dried, to give a solid (200 mg.). A portion (25 mg.) of the solid was converted into the methyl ester methyl glycoside, which was reduced with lithium aluminium hydride. The reduction product was hydrolysed with N-sulphuric acid and chromatographic examination of the hydrolysate showed the presence of 4-*O*-methylglucose, xylose, and glucose (trace).

Methylation of Oat-straw Xylan.—Xylan (17 g.) was methylated ten times with methyl sulphate and sodium hydroxide, and once with methyl iodide and silver oxide. The product (12·6 g.) was fractionated by dissolution in boiling chloroform–light petroleum (b. p. 60—65°) to give a main fraction, soluble in boiling chloroform–light petroleum (30 : 70) (7·4 g.), which had $[\alpha]_D^{17}$ −87·0° (*c* 0·91 in $CHCl_3$) and was used in subsequent experiments (Found: OMe, 38·2%).

Hydrolysis of Methylated Xylan and Separation of Methylated Sugars.—The methylated xylan (5·49 g.) was hydrolysed successively with boiling methanolic 1% hydrogen chloride (600 c.c.) for 30 hr. and with 0·5N-hydrochloric acid (300 c.c.) at 100° for 15 hr. (constant rotation). Evaporation after neutralisation with silver carbonate yielded a syrup (5·99 g.). The syrup (5·93 g.) was fractionated on cellulose (88 × 4 cm.) [13] with light petroleum (b. p. 100—120°)–butan-1-ol (70 : 30), saturated with water, as eluant to give four fractions.

[10] Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289.
[11] Wise, *Ind. Eng. Chem. Anal.*, 1945, **17**, 63.
[12] Hirst and Jones, *J.*, 1949, 1659.
[13] Hough, Jones, and Wadman, *J.*, 1949, 2511.

Fraction 1. Hypoiodite oxidation indicated 95·3% aldopentose, but chromatographic examination in solvent D showed the presence of 2 : 3 : 5-tri-*O*-methylarabinose, 2 : 3 : 4-tri-*O*-methylxylose, and 2 : 3-di-*O*-methylxylose. Although complete separation of the three sugars on filter sheets (Whatman 3MM) with solvent D was not always possible, in one case the three components were completely separated and hypoiodite oxidation showed tri-*O*-methylarabinose and tri- and di-*O*-methylxyloses to be present in the ratios 0·78 : 1·0 : 0·47, corresponding to 96, 124, and 58 mg. respectively of each sugar present in the fraction. Separation of the major part of fraction 1 gave chromatographically pure samples of the two tri-*O*-methylpentoses [fractions 1*a* (36 mg.) and 1*b* (42 mg.)] together with two fractions, containing respectively a mixture of the two tri-*O*-methylpentoses and di-*O*-methylxylose, which were not examined further. Fraction 1*a* had $[\alpha]_D^{19}$ +34·5° (*c* 0·6 in H_2O) and was identified as 2 : 3 : 5-tri-*O*-methyl-L-arabinose by conversion into 2 : 3 : 5-tri-*O*-methyl-L-arabonamide, m. p. and mixed m. p. 136—137°, $[\alpha]_D^{20}$ −16·0° (*c* 1·0 in H_2O), which gave an identical *X*-ray powder photograph (by courtesy of Dr. C. A. Beevers) with that of the authentic amide. Fraction 1*b* crystallised on nucleation with 2 : 3 : 4-tri-*O*-methyl-D-xylose. After recrystallisation from dry ether the sugar had m. p. and mixed m. p. 90—91° and $[\alpha]_D^{18}$ +20° (equil.) (*c* 0·75 in H_2O), and gave an identical *X*-ray powder photograph with that of an authentic specimen. The derived 2 : 3 : 4-tri-*O*-methyl-*N*-phenyl-D-xylosylamine had m. p. and mixed m. p. 95° and $[\alpha]_D^{18}$ +40° (*c* 0·1 in EtOH).

Fraction 2. The chromatographically pure syrup (4·91 g.) was shown by hypoiodite oxidation to be 94% aldopentose (Found : OMe, 34·4. Calc. for $C_7H_{14}O_5$: OMe, 34·8%). Portions of the syrup were seeded with α- and β-forms of 2 : 3-di-*O*-methyl-D-xylose but in both cases the syrup crystallised as 2 : 3-di-*O*-methyl-β-D-xylose.[14] The two crystalline samples had m. p. 78—81°, $[\alpha]_D^{18}$ −20·3° (13 min.) ⟶ +27·8° (240 min., constant) (*c* 0·64 in H_2O), and m. p. 82—84° and $[\alpha]_D^{18}$ −18·1° (12 min.) ⟶ +26·2° (200 min., constant) (*c* 0·7 in H_2O) respectively, and had mixed m. p. 78·5—83·5°. The identity of the sugar was confirmed by conversion into 2 : 3-di-*O*-methyl-*N*-phenyl-D-xylosylamine, m. p. and mixed m. p. 144—145°, and into 2 : 3-di-*O*-methyl-D-xylonamide, m. p. and mixed m. p. 136·5°.

Fraction 3. The syrup (132 mg.) crystallised and had m. p. and mixed m. p. (with 2-*O*-methyl-D-xylose) 132—133° and $[\alpha]_D^{18}$ +34·0° (equil.) (*c* 1·0 in H_2O) (Found : OMe, 18·3. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). Hypoiodite oxidation indicated 93% aldopentose and paper ionophoresis [15] showed that no 3-*O*-methyl-D-xylose was present. The *X*-ray powder photograph was identical with that of an authentic sample and the derived 2-*O*-methyl-*N*-phenyl-D-xylosylamine had m. p. and mixed m. p. 123·5°.

Fraction 4. The syrup (338 mg.), obtained by elution of the cellulose with water, was incompletely soluble in methanol. Purification was effected by dissolution in hot methanol, the insoluble residue was discarded, and the solution was decolorised with charcoal, to give a syrup (293 mg.), $[\alpha]_D^{19}$ +54° (*c* 0·5 in H_2O), R_G 0·12 in solvent C. A portion of the purified syrup (136 mg.) was refluxed for 6 hr. with methanolic 1·5% hydrogen chloride (50 c.c.), neutralised with silver carbonate, and taken to dryness. The resulting syrup was dissolved in dry ether (25 c.c.), and the ethereal solution was added during 3 hr. to a boiling solution of lithium aluminium hydride (250 mg.) in ether (25 c.c.). After a further 2 hr. excess of hydride was destroyed by the addition of water, the solution was acidified with 2N-sulphuric acid and extracted with chloroform, and the chloroform extract was taken to dryness. The resulting syrup (78 mg.) was hydrolysed with 0·5N-hydrochloric acid (30 c.c.) for 8 hr. at 100°, neutralised with silver carbonate, and taken to dryness, to give a syrup (60 mg.). Chromatographic examination of the syrup showed sugars travelling at the same rates as 2 : 3 : 4-tri-*O*-methyl-D-glucose and 3(and/or 2)-methyl-D-xylose, but paper ionophoresis showed that only the 3-methyl ether was present. The major portion of the syrup was fractionated on filter sheets with solvent D, to give fractions *a* (21 mg.) and *b* (28 mg.). Fraction *a* was identified as 2 : 3 : 4-tri-*O*-methyl-D-glucose by conversion into the methyl β-D-pyranoside, m. p. and mixed m. p. 89·5°. Fraction *b* was identified as 3-*O*-methyl-D-xylose by conversion into the aniline derivative, m. p. 136—137°.

Periodate Oxidation of Oat-straw Xylan.—Oxidation of xylan (50 mg. batches) with potassium periodate solution by Halsall, Hirst, and Jones's method [16] gave the following results (expressed as moles of formic acid × 10^3 released per $C_5H_8O_4$ residue) : 7·25 (73 hr.); 8·76 (121 hr.); 9·31 (168 hr.); 11·01 (244 hr.); 12·27 (312 hr.); 15·77 (455 hr.). As the formic acid released did not

[14] Meek, *J.*, 1956, 219.
[15] Consden and Stanier, *Nature*, 1952, **170**, 1069.
[16] Halsall, Hirst, and Jones, *J.*, 1947, 1399, 1427.

reach a constant value, extrapolation to zero time gave a value corresponding to formic acid released from α-glycol scission, namely, 1 mole per 15·7 $C_5H_8O_4$ residues. The release of two mols. of formic acid from the reducing end-group and one mol. from the non-reducing end-group being assumed, this value corresponded to a chain length of 47 residues.

Oxidation of xylan with sodium metaperiodate solution showed that the polysaccharide consumed 1·0 mole of periodate (constant after 334 hr.) per $C_5H_8O_4$ residue. Hydrolysis of the periodate-oxidised polysaccharide showed the presence of a small quantity of xylose.

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NOTES.

222. *The Pyrolysis of 1-Benzylbenzotriazole and Some Homologues thereof.*

By M. S. Gibson.

The Graebe–Ullmann synthesis of carbazoles from 1-phenylbenzotriazoles by pyrolysis indicated that the thermal decomposition of 1-benzylbenzotriazole and its derivatives might provide a convenient route to phenanthridines:

1-Benzylbenzotriazole, prepared by a modification of the method of Krollpfeiffer, Pötz, and Rosenburg,[1] was found to be very stable to pyrolysis. Slow decomposition occurred at 350—400°, or in phosphoric acid solution [2] at 220°, but gave only indefinite or carbonaceous material. When, however, the triazole was heated with a little copper powder at 350—400° under nitrogen, phenanthridine was isolated in small yield as picrate, together with (probably) toluene.

Alkylation of benzotriazole with 2- and 4-methylbenzyl chloride gave respectively 1-2′- and 1-4′-methylbenzylbenzotriazole; these have the expected ultraviolet absorptions.[1] Pyrolysis gave 8- and 6-methylphenanthridine, together with (probably) *o*- and *p*-xylene, respectively.

As an alternative route to the 1-benzylbenzotriazoles, *o*-chloronitrobenzene was condensed with benzylamine by a modification of Kehrmann and Tichvinsky's method.[3] Reduction to the diamine, followed by treatment with nitrous acid, afforded 1-benzylbenzotriazole, together with a large amount of tar. An attempt to prepare 1-2′-methylbenzylbenzotriazole by analogous reactions failed.

Experimental.—*1-Benzylbenzotriazole.* A hot solution of benzotriazole (5 g.) in ethanol (18 c.c.) was added to sodium ethoxide (from sodium, 1 g.) in ethanol (14 c.c.) on the steam-bath. After 5 min., benzyl chloride (5·4 g.) in ethanol (8 c.c.) was added, and the mixture was heated on the steam-bath for 3 hr. The precipitated sodium chloride was removed, and the filtrate evaporated. Crystallisation of the residue from methanol afforded 1-benzylbenzotriazole as prisms, m. p. 115—116°. Krollpfeiffer *et al.*[1] give m. p. 115—116°.

Pyrolysis. 1-Benzylbenzotriazole (4 g.) with a trace of copper powder was heated at 350—400° under nitrogen. Small quantities of volatile material were allowed to escape from time

[1] Krollpfeiffer, Pötz, and Rosenburg, *Ber.*, 1938, **71**, 596.
[2] Robinson and Thornley, *J.*, 1924, 2169.
[3] Kehrmann and Tichvinsky, *Annalen*, 1896, **290**, 293.

to time. The reaction was judged to be complete when no more volatile material was formed (5—6 hr.). The dark product was extracted with hot dilute hydrochloric acid (charcoal), and picric acid was added to the filtrate. The precipitated phenanthridine picrate formed yellow needles (from water), m. p. and mixed m. p. 244—245° (Found: C, 56·2; H, 3·0. Calc. for $C_{19}H_{12}O_7N_4$: C, 55·9; H, 2·9%). **9**: 10-Dihydrophenanthridine [4] gave a picrate, red needles (from ethanol), m. p. 238° (Ritchie [5] gives m. p. 238°), depressed to 218—223° (decomp.) on admixture with the foregoing picrate.

1-2′-*Methylbenzylbenzotriazole.* Benzotriazole (10 g.) was alkylated with 2-methylbenzyl chloride [6] (12 g.), as in the previous case. From methanol, 1-2′-*methylbenzylbenzotriazole* (15 g.) separated as cubes, m. p. 84—85° (Found: C, 75·7; H, 5·8; N, 18·8. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·8; N, 18·9%).

8-*Methylphenanthridine picrate.* The foregoing triazole (10 g.), pyrolysed as above, gave an orange-brown oil, b. p. 170—270°/17 mm., which was dissolved in ether and extracted with dilute hydrochloric acid. The acid extract (charcoal) was basified and extracted with ether. Addition of picric acid to the dried ethereal solution precipitated 8-*methylphenanthridine picrate* (400 mg.), which crystallised from water in yellow needles, m. p. 253—254° (Found: C, 56·7; H, 3·5; N, 13·0. $C_{20}H_{14}O_7N_4$ requires C, 56·9; H, 3·3; N, 13·3%).

The volatile material (1 g.) collected during the pyrolysis was distilled, and a fraction (650 mg.), b. p. 142—146°, smelling of *o*-xylene was collected. This was oxidised by means of potassium permanganate and sodium hydroxide solutions to phthalic acid, m. p. 190—200° (anhydride, m. p. and mixed m. p. 128—129°).

6-*Methylphenanthridine picrate.* Benzotriazole (10 g.) and 4-methylbenzyl chloride [7] (12 g.) similarly yielded 1-4′-*methylbenzylbenzotriazole* (14 g.), needles (from methanol), m. p. 106—107° (Found: C, 75·4; H, 5·9%). Treated as above, this triazole (10 g.) gave 6-*methylphenanthridine picrate* (350 mg.), yellow needles (from water), m. p. 245—246° (Found: C, 57·3; H, 3·6; N, 13·0%).

Redistillation of the volatile material (900 mg.) evolved during the pyrolysis afforded a fraction (500 mg.), b. p. 140—145°, smelling of *p*-xylene; this was oxidised as in the previous case and the resulting terephthalic acid converted by way of the chloride into the dimethyl ester, needles (from methanol), m. p. and mixed m. p. 139—140°.

N-o-*Nitrophenylbenzylamine.* The following modification of the known method [8] gave an enhanced yield. A stirred mixture of *o*-chloronitrobenzene (16 g.), benzylamine (10·5 g.), and anhydrous potassium carbonate (7 g.) was heated at 150° for 2 hr., then cooled, powdered, and extracted with boiling ethanol. The concentrated extract deposited the amine (18 g.) as orange prisms, m. p. 74—75°. Kehrmann and Messinger [8] record m. p. 74—75°.

A solution of stannous chloride (65 g.) in concentrated hydrochloric acid (200 c.c.) at 100° was cautiously added to one of this amine (16 g.) in boiling acetic acid. An excess of sodium hydroxide solution was added to the cooled mixture, and the precipitated solid was collected and extracted with boiling ethanol. The filtrate was also washed with ether, the extract being concentrated and the residue added to the ethanolic extract already obtained. Water (80 c.c.) and concentrated hydrochloric acid (100 c.c.) were added to the ethanolic solution, and, after cooling to 0—5°, a solution of sodium nitrite (6 g.) in water (12 c.c.) was added with stirring. An intense red colour developed, and much tar separated. The mixture was rendered slightly alkaline by 5% sodium hydroxide solution. The dark semi-solid material was collected and washed with water; four crystallisations from aqueous methanol (charcoal) afforded 1-benzylbenzotriazole (1 g.) as pale buff prisms, m. p. and mixed m. p. 115—116°.

2-*Methyl*-N-o-*nitrophenylbenzylamine.* 2-Methylbenzylamine (15 g.), b. p. 80—82°/15 mm., was prepared by hydrogenation of *o*-tolunitrile (20 g.) in ethanol (120 c.c., saturated with ammonia at 0°) with Raney nickel at 100°/120 atm. Under analogous conditions, *p*-tolunitrile (20 g.) gave 4-methylbenzylamine (16 g.), b. p. 82—83°/15 mm. Hydrogenolysis of *N*-benzyl linkages appeared to be comparatively slow under these conditions.

Condensation of *o*-chloronitrobenzene (16 g.) with 2-methylbenzylamine (12 g.) in presence of potassium carbonate (7 g.) was effected at 160—165° (2 hr.). Isolated as in the earlier case, 2-*methyl*-N-o-*nitrophenylbenzylamine* (18 g.) separated from ethanol in orange prisms, m. p. 103—104° (Found: C, 69·6; H, 5·9; N, 11·6. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8; N, 11·6%).

[4] Wooten and McKee, *J. Amer. Chem. Soc.*, 1949, **71**, 2946.
[5] Ritchie, *J. Proc. Roy. Soc. New South Wales*, 1945, **78**, 177.
[6] Smith and Spillane, *J. Amer. Chem. Soc.*, 1940, **62**, 2639.
[7] Blanc, *Bull. Soc. chim. France*, 1923, **33**, 313.
[8] Kehrmann and Messinger, *J. prakt. Chem.*, 1892, **46**, 565.

The *acetyl derivative* crystallised from aqueous ethanol in colourless plates, m. p. 124—125° (Found : C, 67·7; H, 5·7; N, 9·8. $C_{15}H_{16}O_3N_2$ requires C, 67·6; H, 5·6; N, 9·9%).

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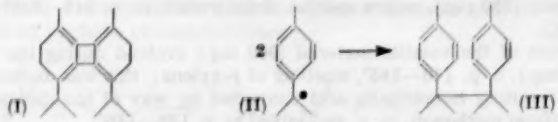
223. *Structure of a By-product in the Formation of Ascaridole Glycol Anhydride.*

By A. H. BECKETT and G. O. JOLLIFFE.

IN the preparation of ascaridole glycol anhydride by dropwise addition of ascaridole to boiling *p*-cymene, Thoms and Dobke [1] reported the presence of a crystalline by-product, $C_{20}H_{28}$, m. p. 158°, to which they tentatively assigned formula (I). Under similar conditions we obtained a compound, $C_{20}H_{26}$, m. p. 157° which was identified as 2 : 3-dimethyl-2 : 3-di-*p*-tolylbutane (III). The by-product was probably formed by the dimerisation of two free radicals of dimethyl-*p*-tolylmethyl (II) the formation of which from *p*-cymene was initiated by the presence of ascaridole.



2 : 3-Dimethyl-2 : 3-di-*p*-tolylbutane was prepared by bubbling oxygen through specially purified *p*-cymene in the presence of a catalyst ; [2] the use of commercial samples of *p*-cymene, even after fractional distillation, gave gummy residues instead of the desired product.

Experimental.—By-product in the formation of ascaridole glycol anhydride. A solution of ascaridole (30 g.) (purified by the method of Beckett *et al.*[3]) in *p*-cymene (60 g.) (purified by the method of Pines *et al.*[2]) was added dropwise to *p*-cymene (40 g.) boiling under reflux, and the mixture refluxed for 18 hr. Subsequent distillation gave *p*-cymene, b. p. 78—80°/25 mm., ascaridole glycol anhydride, b. p. 79—80°/0·5 mm., and a residue which recrystallised from ethanol as needles, m. p. 157° (0·49 g.), and was 2 : 3-dimethyl-2 : 3-di-*p*-tolylbutane [Found : C, 90·2, 90·5; H, 9·7, 9·7%; *M* (ebullioscopic in acetone), 257, 259. Calc. for $C_{20}H_{26}$: C, 90·2; H, 9·8%; *M*, 266].

The m. p. and the infrared and the ultraviolet absorption curve of the above crystalline product were identical with those of 2 : 3-dimethyl-2 : 3-di-*p*-tolylbutane prepared as reported below ; a mixture of the latter with the crystalline product was undepressed in m. p.

p-Cymene (100 g.) alone, or with ascaridole (1 g.), when refluxed as above gave 35 and 54 mg. respectively of 2 : 3-dimethyl-2 : 3-di-*p*-tolylbutane. Refluxing *p*-cymene (100 g.) alone, and *p*-cymene (100 g.) with ascaridole glycol anhydride (10 g.), both in the dark, gave negligible residues of by-product.

2 : 3-*Dimethyl*-2 : 3-*di*-p-*tolylbutane.* As described by Pines *et al.*,[3] *p*-cymene (60 g.) was heated with coarse aluminium powder (50 g.) and anhydrous potassium carbonate (2 g.) under reflux for 18 hr. whilst oxygen was bubbled in at the rate of 12 l./hr., giving 2 : 3-dimethyl-2 : 3-di-*p*-tolylbutane (0·9 g.), m. p. 157°.

Oxidation. Oxidation [4] of the by-product (100 mg.), and of 2 : 3-dimethyl-2 : 3-di-*p*-tolylbutane (100 mg.), with nitric acid (3 ml. 25% w/w) at 190° for 18 hr. gave residues (75 mg.)

[1] Thoms and Dobke, *Arch. Pharm.*, 1930, **268**, 128.
[2] Pines, Kvetinskas, and Ipatieff, *J. Amer. Chem. Soc.*, 1955, **77**, 343.
[3] Beckett, Donbrow, and Jolliffe, *J. Pharm. Pharmacol.*, 1955, **7**, 55.
[4] Campbell, Soffer, and Steadman, *J. Amer. Chem. Soc.*, 1942, **64**, 426.

which, after being washed and dried, had m. p. >300° (with sublimation) and equiv. 84·0 and 83·7 respectively [Calc. for $C_6H_4(CO_2H)_2$: equiv., 83·0]. The dimethyl esters had m. p. 140° alone or mixed with dimethyl terephthalate.

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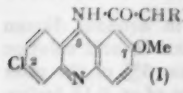
224. 2-*Chloro*-5-α-*halogenoacylamino*-7-*methoxyacridines*.

By M. NEEMAN.

5-AMINO-2-CHLORO-7-METHOXYACRIDINE was acylated with α-halogenoacyl halides to yield the amides (I; R = H or Me, X = Cl or Br). The α-halogen atom in (I; R = H, X = Cl or Br) did not react with boiling diethylamine, in contrast to the analogous 6-methoxy-8-halogenoacetamidoquinolines.[1]



(I)

Experimental.—*2-Chloro-5-chloroacetamido-7-methoxyacridine* (I; R = H, X = Cl) was prepared by the addition of chloroacetyl chloride (1·1 g., 0·01 mol.) in chloroform (10 ml.) at −5° to a suspension of finely powdered 5-amino-2-chloro-7-methoxyacridine (2·6 g., 0·01 mol.) in chloroform (20 ml.) and pyridine (1 ml.). After 15 hr. at 30°, the product was filtered off, washed with dilute aqueous ammonia and water, and crystallised from 60% formic acid as yellow needles, m. p. 315° (decomp.) (Found: C, 56·9; H, 3·9; N, 8·6. $C_{16}H_{13}O_2N_3Cl_2$ requires C, 57·3; H, 3·6; N, 8·4%).

5-Bromoacetamido-2-chloro-7-methoxyacridine (I; R = H, X = Br) was prepared in an analogous manner by using bromoacetyl bromide, and crystallised from 60% formic acid in yellow needles, m. p. 330° (decomp.) (Found: C, 50·4; H, 3·6; N, 7·5. $C_{16}H_{12}O_2N_3BrCl$ requires C, 50·6; H, 3·2; N, 7·4%).

Both halogenoacetamido-compounds were recovered unchanged after 30 hours' refluxing with excess of diethylamine.

5-α-Bromopropionamido-2-chloro-7-methoxyacridine (I; R = Me, X = Br) was prepared in an analogous manner by using α-bromopropionyl bromide, and crystallised from acetone–ethanol as yellow needles, decomp. >360° (Found: C, 51·5; H, 4·0. $C_{17}H_{14}O_2N_3BrCl$ requires C, 51·8; H, 3·6%).

RESEARCH COUNCIL OF ISRAEL, JERUSALEM.

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[1] Neeman, *J.*, 1955, 2525.

225. *Tracer Studies on Ester Hydrolysis. Part III.* The Alkaline Hydrolysis of Phenyl Benzoate.*

By C. A. BUNTON and D. N. SPATCHER.

IN some recent work [1] the alkaline hydrolysis of phenyl benzoate enriched in ^{18}O was used to locate the position of the tracer. It was assumed that one oxygen atom of the benzoic acid came from the water and the other from the ester, *e.g.*,

$$Ph{\cdot}C^{18}O{\cdot}OPh + OH^- \longrightarrow Ph{\cdot}C^{18}O{\cdot}O^- + Ph{\cdot}OH$$

This assumption has been tested by hydrolysing phenyl benzoate with sodium hydroxide, at 0°, in 50% aqueous dioxan, with the water isotopically enriched in ^{18}O. At intervals, unhydrolysed ester was isolated and its isotopic abundance measured. There

* Part II, *J.*, 1955, 1522.

[1] Bunton, Lewis, and Llewellyn, *J.*, in the press.
[2] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626.

was no appreciable oxygen exchange with water, whereas for the hydrolysis of alkyl benzoates the exchange rate is *ca.* 20% of that of hydrolysis.[2]

$$R'\cdot CO_2R + {}^{18}OH^- \rightleftharpoons R'\cdot C(O^-)({}^{18}OH)\text{–}OR \longrightarrow R'\cdot CO_2^- + ROH$$

(I.)

Therefore the intermediate (I), if formed, either loses the phenoxide rather than the hydroxide ion, or its life is too short for the two oxygen atoms to become equivalent by proton transfer. The present experiments do not differentiate between these possibilities. To allow calculation of the extent of hydrolysis the kinetics were followed over a limited range of alkali concentration; this alkaline hydrolysis of phenyl benzoate is much faster than that of the alkyl benzoates. The acid reaction is very slow.

Experimental.—The hydrolyses were followed by acid–base titration in aqueous dioxan (50% by volume), at 0°. Preliminary experiments showed that the reaction in acid solution was much slower than with hydroxyl ion; with N/40-hydrochloric acid, *ca.* 5% of the ester decomposed in 20 hr. at 25°. The reaction was therefore stopped by addition of *ca.* 0·1N-hydrochloric acid which was back-titrated, methyl-red–bromocresol-green being used. The rate coefficients were calculated graphically from the equation $k_2t(b - 2a) = \log_e a(b - 2x)/b(a - x)$, where a and b were the initial molar concentrations of ester and hydroxyl ion, respectively, and $(a - x)$ was the molar concentration of ester at time t. An example of a kinetic run is given below.

Temp. 0°; [Ester] = 0·0294M; [OH^-] = 0·0874M

Time (min.)		3·5	5	7	10	14	20	30
Reaction (%)		24·1	28·9	34·8	42·5	49·5	58·1	68·0
$\log_{10}\frac{b-2x}{a-x}$	found	0·5152	0·5275	0·5424	0·5664	0·5930	0·6355	0·7028
	reqd.	0·5150	0·5270	0·5410	0·5630	0·5920	0·6360	0·7060

$10^3k_2 = 9·9$ mole^{-1} l. sec.$^{-1}$.

The second-order rate coefficients (which were dependent on [OH^-]) were :

Run	[Ester], M	[OH^-], M	10^3k_2 (mole^{-1} l. sec.$^{-1}$)
1	0·0262	0·0435	13·0
2	0·0294	0·0874	9·9
3	0·0295	0·0965	9·7

Isolation of unchanged ester. Hydrolysis was carried out under kinetic conditions, with water enriched in ^{18}O. At intervals, reaction was stopped by addition of excess of hydrochloric acid, and the precipitated ester washed and recrystallised from aqueous alcohol. The purified esters were pyrolysed, over carbon *in vacuo*, to carbon monoxide, and this gas analysed mass-spectrometrically. A run, carried out under the conditions of kinetic run 1 and with the isotopic abundance of the water 0·383 atom-% excess, gave ester, isolated at various values of % reaction, with the following excess of isotopic abundances, 15% reaction, 0·003%; 35% reaction, 0·005%; 55% reaction, 0·005%; 75% reaction, 0·006%. A second run with [Ester] = 0·04M, [OH^-] = 0·129M, and isotopic abundance of water = 2·80 atom-% excess, gave ester (m. p. 69°), isolated at 75% reaction, of 0·002 atom-% excess. In a confirmatory experiment a sample of benzoic acid (m. p. 121°) was isolated from an alkaline hydrolysis, with enriched water (isotopic abundance, 0·525 atom-% excess) its abundance was 0·260 atom-% excess.

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226. *Some Reactions in the Phthalazine Series.*

By C. M. Atkinson, C. W. Brown, and (the late) J. C. E. Simpson.

The preparation of 1-aminophthalazine (I; R′ = H, R = NH_2) has not been described although some physical constants are recorded.[1] Systematic investigation of the reaction conditions was needed before 1-chlorophthalazine (I; R′ = H, R = Cl) was prepared in consistently good yields from the hydroxy-compound. 1-Phenoxyphthalazine (I; R′ = H, R = OPh), prepared from the chloro-compound, was converted into the amine. As expected, 1-chlorophthalazine was stable to alkali at room temperature but with 5N-hydrochloric acid gave the hydroxy-compound, whereas more dilute acid yielded a compound which has been represented [2] by the structure (II) since the completion of this work.

1-Acetamidophthalazine was obtained from the amine by use of pyridine–acetic anhydride (but not of acetic anhydride alone) and readily formed a methiodide which on acid hydrolysis gave 1-aminophthalazine methiodide, identical with that prepared directly from the base.

1-Amino-7-nitrophthalazine (I; R′ = NO_2, R = NH_2) was prepared by a similar route to that leading to the *Bz*-unsubstituted compound. The nitrophthalaldehydic acid was prepared by the known method [3] but with modified bromination of 6-nitrophthalide. 1-Hydroxy-7-nitrophthalazine (I; R′ = NO_2, R = OH) was converted by phosphoryl chloride into the 1-chloro-derivative which resinified on attempted recrystallisation. As in the case of the *Bz*-nitro-4-phenoxycinnolines,[4] 7-nitro-1-phenoxyphthalazine (I; R′ = NO_2, R = OPh) was best prepared by using ammonium carbonate (rather than potassium hydroxide) in phenol. The phenoxy-compound, on treatment with molten ammonium acetate, gave 1-amino-7-nitrophthalazine which behaved as did the *Bz*-unsubstituted compound toward acetylating reagents and provided a dark red methiodide.

Experimental.—*1-Chlorophthalazine.* The hydroxy-compound (5 g.; m. p. 181—182°) was heated with phosphoryl chloride (15 c.c.) until boiling began. Refluxing was continued for *ca.* 2 min. Solid began to separate. The mixture was shaken until precipitation was complete (4 min.), then was poured into stirred 2N-sodium hydroxide (500 c.c.) and crushed ice (500 c.c.). The chloro-compound (4·2—4·7 g.), m. p. 109—111°, was washed with water and dried *in vacuo* over sodium hydroxide. In 7 of 8 experiments the yield was >70% (average 78%). Shorter heating reduced the yield. Gabriel and Neumann's [5] conditions never gave a yield of more than 46% (they claim 75%).

1-Phenoxyphthalazine. Finely powdered 1-chlorophthalazine (4·4 g.) was heated with potassium hydroxide (1·8 g., 1·2 mols.) in phenol (30 g., 7·5 mols.) on the steam-bath for 1 hr., cooled, and poured into 40% sodium hydroxide solution. The clear solution was diluted to *ca.* 300 c.c. and the yellow granular product (5·4 g., 91%) was collected. Pure *1-phenoxyphthalazine*, m. p. 107—108°, was obtained by recrystallisation from ethanol (Found: C, 75·6; H, 4·75; N, 12·8. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5; N, 12·6%).

1-Aminophthalazine. Crude 1-phenoxyphthalazine (4 g.) was heated with molten ammonium acetate at 150—160° for 30 min. The amino-compound (2·5 g., 92%), m. p. 212—213°, was isolated by trituration of the cold mixture with water, in which the amine is appreciably soluble. Recrystallisation from nitromethane gave pure *1-aminophthalazine*, m. p. 212—213°, as colourless needles (Found: C, 66·1; H, 5·0; N, 29·0. $C_8H_7N_3$ requires C, 66·2; H, 4·9; N, 28·9%).

[1] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[2] Badger, McCarthy, and Rodda, *Chem. and Ind.*, 1954, 964.
[3] Borsche, Diacont, and Hanau, *Ber.*, 1934, **67**, 675.
[4] Keneford and Simpson, *J.*, 1948, 354.
[5] Gabriel and Neumann, *Ber.*, 1893, **26**, 521.

To a suspension of the amine (1 g.) in pyridine (8 c.c.) was added acetic anhydride (3 c.c.), and the mixture set aside for 3 hr., then evaporated to dryness in a desiccator, and the product isolated by treatment with acetone. 1-*Acetamidophthalazine*, m. p. 183—184°, separated from ethanol in colourless needles (Found: C, 64·1; H, 4·7; N, 22·9. $C_{10}H_9ON_3$ requires C, 64·15; H, 4·8; N, 22·45%). Heating this (0·21 g.) with ethanol (4 c.c.) and methyl iodide (2 c.c.) gave the *methiodide* which separated from water as pale yellow rods, m. p. 253—254° (depressed to 220° on admixture with the 1-amino-salt, m. p. 251—252°) (Found: C, 40·45; H, 3·75; N, 13·0; I, 43·95. $C_{11}H_{12}ON_3I$ requires C, 40·15; H, 3·7; N, 12·8; I, 38·6%).

1-*Aminophthalazine methiodide*. (*a*) The amino-compound (1 g.), methanol (5 c.c.), and methyl iodide (2 c.c.) were refluxed for 4 hr. and the solution was set aside for crystallisation (30 min.; 0·73 g.). Recrystallisation from water gave the *methiodide*, m. p. 251—252° (0·68 g.), as pale yellow needles (Found: C, 37·7; H, 3·65; N, 14·5; I, 43·05. $C_9H_{10}N_3I$ requires C, 37·6; H, 3·5; N, 14·6; I, 44·2%). The mother liquor yielded unchanged base (0·49 g.), m. p. 200—205°.

(*b*) 1-Acetamidophthalazine methiodide (0·15 g.) was refluxed with N-hydrochloric acid (1 c.c.) for 1 hr., the solution was cooled, and the methiodide (0·1 g.), m. p. and mixed m. p. 251—252°, collected.

2-*Formyl*-5-*nitrobenzoic acid*. 6-Nitrophthalide (14·4 g.)[3] was kept at 175—180° and bromine (10·6 c.c.) passed in during 2 hr. in a stream of carbon dioxide. The dark red resinous product was boiled with water (*ca.* 200 c.c.) for 45 min. (a small amount of insoluble tar remained) and treated with carbon. The aldehydo-acid separated as pale yellow needles (10·1 g.), m. p. 156—160°. The acid yielded a 2 : 4-dinitrophenylhydrazone, m. p. 288—290° (decomp.) (lit., m. p. 290°). The recorded method of bromination[3] gave only unchanged material.

1-*Hydroxy*-7-*nitrophthalazine*. A solution of the above acid (10·1 g.) in 95% ethanol (300 c.c.) was heated with 36·5% aqueous hydrazine (4·6 c.c.) for 1 hr. The *phthalazine* (7·6 g.), m. p. 232—233°, separated on cooling (Found: C, 50·45; H, 2·55; N, 22·05. $C_8H_5O_3N_3$ requires C, 50·3; H, 2·6; N, 22·0%). This compound is insoluble (sodium salt) in 2N-sodium hydroxide but soluble in more dilute (*ca.* N/30) alkali; it crystallises from ethanol or nitromethane as pale yellow needles.

1-*Chloro*-7 *nitrophthalazine*. The hydroxy-compound (3 g.) was heated on the steam-bath for 1 hr. with phosphoryl chloride (9 c.c.), and the mixture poured into stirred aqueous sodium hydroxide (300 c.c.) and crushed ice (300 c.c.). The pale yellow solid was extracted with chloroform and the extract washed with 2N-sodium hydroxide and water, dried, and evaporated to give the crude chloro-compound (2·55 g.), m. p. 155—157° (decomp.).

7-*Nitro*-1-*phenoxyphthalazine*. The foregoing chloro-compound (4·8 g.), ammonium carbonate (6·5 g.), and phenol (14·4 g.) were heated on the steam bath for 45 min. and poured into 2N-sodium hydroxide. The brown solid formed from the initial oil was filtered off and yielded material, m. p. 204—207° (5·05 g.), by successive digestion with small portions of water and ethanol. The *phenoxy-compound*, m. p. 212—213°, separated from chloroform–light petroleum (b. p. 60—80°) as pale yellow needles (Found: C, 62·75; H, 3·4; N, 15·65. $C_{14}H_9O_3N_3$ requires C, 62·9; H, 3·4; N, 15·7%).

1-*Amino*-7-*nitrophthalazine*. This was prepared from the phenoxy-derivative (2·4 g.) as for the *Bz*-unsubstituted compound (185—190° for 15 min.). The melt was cooled, diluted with water, and basified with concentrated aqueous ammonia, and the solid was purified by dissolution in 30—40% acetic acid (charcoal) and precipitation by ammonia. The resulting bright yellow granular *amine* (1·4 g.) crystallised from aqueous methanol as needles, m. p. 303—304° (decomp.) (Found: C, 48·4; H, 3·95; N, 27·75. $C_8H_6O_2N_4,\frac{1}{2}H_2O$ requires C, 48·2; H, 3·5; N, 28·1%). This gave, as above, the *acetyl derivative*, yellow needles, m. p. 252—253° (from methanol) (Found: C, 52·05; H, 3·5; N, 24·2. $C_{10}H_8O_3N_4$ requires C, 51·65; H, 3·5; N, 24·1%).

1-*Amino*-7-*nitrophthalazine methiodide*, prepared in the usual manner and recrystallised (3 times) from water, had m. p. 251—252° (Found: C, 32·75; H, 2·75; N, 16·8; I, 38·45. $C_9H_9O_2N_4I$ requires C, 32·6; H, 2·7; N, 16·9; I, 38·2%).

2-*Methyl*-7-*nitro*-1-*phthalazone*. A solution of 1-hydroxy-7-nitrophthalazine (0·2 g.) in 0·5N-sodium hydroxide (3 c.c.) and water (40 c.c.) was shaken with methyl sulphate (0·1 c.c.) and set aside for 15 min. after pale yellow needles (0·11 g.) began to separate. The pure *phthalazone*, m. p. 177—179°, crystallised from ethanol (Found: C, 53·1; H, 2·95; N, 20·5. $C_9H_7O_3N_3$ requires C, 52·7; H, 3·4; N, 20·5%).

1-*Methoxy*-7-*nitrophthalazine*. Crude 1-chloro-7-nitrophthalazine (0·15 g.), methanol (3 c.c.) and methanolic sodium methoxide (3 c.c. containing 0·045 g. of methoxide) were refluxed for 30 min., then poured into water. Extraction with ether and evaporation of the washed, dried,

and clarified (charcoal) extract left a sticky solid (0·12 g.). Repeated recrystallisation from aqueous ethanol gave the ***methoxy-derivative***, m. p. 175—176°, as light brown needles (Found : C, 52·9; H, 3·95; N, 20·6. $C_9H_7O_3N_3$ requires C, 52·7; H, 3·4; N, 20·5%). A mixed m. p. with the isomeric phthalazone (above) was 130—135°.

The authors thank Mr. E. S. Morton and Mr. H. Swift for the microanalyses.

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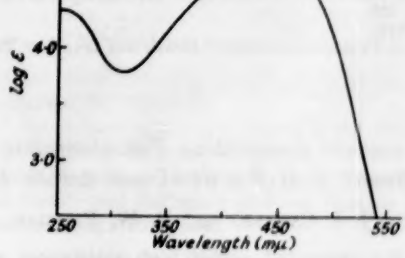
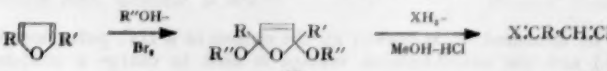
227. *Ultraviolet Absorption Spectra of 2 : 4-Dinitrophenylhydrazones of Conjugated Alkenediones.*

By K. G. LEWIS.

DURING work involving a reaction with 2 : 4-dinitrophenylhydrazine, a substance was isolated for which one possible formulation was the bis-2 : 4-dinitrophenylhydrazone of a compound of type R·CO·CH:CH·CO·R′ (I). Although the ultraviolet absorption spectra of the 2 : 4-dinitrophenylhydrazones of conjugated unsaturated monocarbonyl compounds



are well established,[1,2] there appeared to be no record of ultraviolet absorption spectra of 2 : 4-dinitrophenylhydrazones derived from the type of compound (I). Compounds having the required absorbing system were readily prepared by the following route :



(II) (III)

[X = $(NO_2)_2C_6H_3$·NH·N=.]

The absorption curve for the compound (III ; R = H, R′ = CH_2·OMe) in dioxan is shown in the Figure ; curves for three other substances were very similar. They show no well-defined peak, only a broad intense band in the region 400—460 mμ (log ε 4·6—4·7) and this seems characteristic of this conjugated chromophore.

Experimental.—*2 : 5-Dialkoxy-2 : 5-dihydrofurans.* Except the parent (II ; R = R′ = H) these were prepared by the action of bromine and methanol on the corresponding furan according to the directions of Clauson-Kaas.[3] The parent (II ; R = R′ = H) was prepared

[1] Braude and Jones, *J.*, 1945, 498.
[2] Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy," Arnold, London, 1954.
[3] Clauson-Kaas, *Kgl. danske Videnskab. Selskab, Mat.-fys. Medd.*, 1947, **24**, 6.

by Mr. V. R. Stimson by the action of *tert.*-butyl hypochlorite in *tert.*-butanol on furan, which gave no isolable product with bromine and *tert.*-butanol. 2 : 5-Dihydro-2 : 5-dimethoxy-2-methylfuran had b. p. 61—62°/20 mm., n_D^{22} 1·4296 (lit.,[4] b. p. 46°/8 mm., n_D^{25} 1·4265) (Found : C, 58·6; H, 8·8; OMe, 41·3. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·4; OMe, 43·0%). 2 : 5-Dihydro-2 : 5-dimethoxy-2-methoxymethylfuran had b. p. 92°/15 mm., n_D^{17} 1·4430 (lit.,[5] 84—85°/10 mm., n_D^{25} 1·4383) (Found : C, 55·3; H, 8·1. Calc. for $C_8H_{14}O_4$: C, 55·2; H, 8·1%).

Bis-2 : 4-*dinitrophenylhydrazones of alkenediones.* The dialkoxydihydrofuran (0·5 ml.) was added dropwise to 2 : 4-dinitrophenylhydrazine (1 g.) in boiling methanol (100 ml.) containing concentrated hydrochloric acid (1 ml.). The red powder that slowly separated was washed with methanol and recrystallised, yielding red *bis*-2 : 4-*dinitrophenylhydrazones* of malealdehyde, needles (from nitromethane), m. p. 300° (decomp.) (Found : C, 43·2; H, 2·9. $C_{16}H_{12}O_8N_8$ requires C, 43·25; H, 2·7%), 4-oxopent-2-enal, needles (from nitrobenzene–tetrachloroethane), m. p. 269° (decomp.) (Jones[6] records m. p. 270°) (Found : C, 45·1; H, 3·2; O, 27·6; N, 24·1. Calc. for $C_{17}H_{14}O_8N_8$: C, 44·5; H, 3·1; O, 27·95; N, 24·45%); 5-methoxy-4-oxopent-2-enal (from nitrobenzene–tetrachloroethane), m. p. 259° (decomp.) (Found : C, 44·1; H, 3·5; OMe, 6·0. $C_{18}H_{16}O_9N_8$ requires C, 44·3; H, 3·3; OMe, 6·35%), and hex-3-ene-2 : 5-dione, needles (from nitromethane), m. p. 289—289·5° (decomp.) (Jones[6] records m. p. 290°) (Found : C, 46·0; H, 3·4. Calc. for $C_{18}H_{16}O_8N_8$: C, 45·8; H, 3·4%).

Absorption spectra were measured on a Hilger Uvispek. Dioxan was purified as recommended by Fieser.[7]

The microanalyses were carried out by Dr. K. W. Zimmermann of the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

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ARMIDALE, N.S.W., AUSTRALIA. [*Received, November 3rd,* 1955.]

[4] Clauson-Kaas, Limborg, and Dietrich, *Acta Chem. Scand.*, 1952, **6**, 545.
[5] Clauson-Kaas, *ibid.*, p. 556.
[6] Jones, B.P., 595,041/1945.
[7] Fieser, "Experiments in Organic Chemistry," Heath and Co., New York, 2nd Edn., p. 369.

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228. *A Direct-current Integrating Potentiometric Circuit for the Measurement of Small E.M.F.s developed across High Resistances.*

By J. I. CARASSO and R. W. PITTMAN.

MEASUREMENTS of E.M.F.s generated across high resistances are usually made with instruments involving electrometer triodes, as in commercial pH meters. An alternative method is described here which has been found advantageous for measurements on sources with resistances up to 10^{10} ohms such as specimens of grey selenium and some special glass electrodes.

The E.M.F. to be measured, E, is backed by the output of a D.C. potentiometer (Tinsley G.P. Type 3387B.) and the out-of-balance voltage is used to charge a condenser (T.C.C. "Plastapack," Type C.P.L.) for a time depending on the time-constant of the resistance–capacity circuit consisting of the source, R, and condenser, C (Fig. 1). The deflection obtained on discharging the condenser through a ballistic galvanometer, G, is plotted against the backing voltage, and the required E.M.F. is given by the intercept of the plot on the voltage axis.

The circuit must be efficiently guarded against stray charging currents which cause misleading results; adequate protection to obtain results for source resistances up to 10^9 ohms can be achieved by standing the apparatus on an earthed metal plate and using earthed-screen leads. If due allowance is made for the residual stray charging current (always $<10^{-12}$ A), E from sources of 10^{10} ohms can be measured to the nearest mV.

An estimate of the resistance of the source may be obtained from a ballistic measurement of the time-constant of the resistance–capacity circuit.

The quality of the results justifies the greater expenditure of time and the need to use a sensitive ballistic galvanometer. As shown in Fig. 2, it is possible to measure a potential difference across a source of resistance 10^{10} ohms to the nearest 1 mV, *i.e.*, to detect a power

of 10^{-16} w, a 4500 mm./μc galvanometer and a 0·1 μF condenser being used with allowance of a charging time of *ca.* 1 min.

If the resistance of the source does not exceed 10^8 ohms, measurements to the nearest 0·05 mv can readily be obtained with a 2 μF condenser. When an electronic pH meter, fitted with an external reflecting galvanometer, was used as a voltmeter across sources with

FIG. 1.

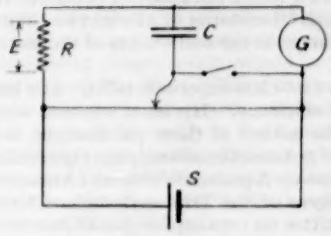
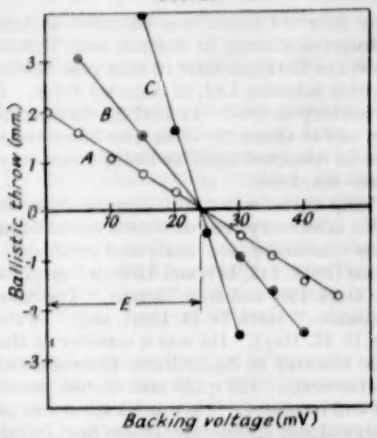


FIG. 2.



Charging time: *A*, 30 sec.; *B*, 1 min.; *C*, 2 min. $R = 10^{10}$ ohms. $C = 0{\cdot}1$ μF.

resistances as low as 5×10^7 ohms, readings could not be taken with an accuracy better than $\pm 0{\cdot}5$ mv owing to external interferences.

Part of the success of the method appears to reside in the time integration of the total input signal, which cancels much of the random " noise " inherent in such measurements. The successful use of this simple principle is probably largely due to the excellent insulation resistance (over 10^6 ohm farad) and negligible residual charges and anomalous charging currents of the polystyrene film capacitors used.

One of us (J. I. C.) is indebted to the Engineer-in-Chief of the General Post Office for permission to use this information.

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[*Received, November 23rd, 1955*]

OBITUARY NOTICES.

PHILIP RUFUS CARTER.

1921—1955.

Philip Rufus Carter was educated at Latymer Upper School, from which he proceeded to the Imperial College of Science and Technology in 1939. He graduated with Second Class Honours in 1941 and later in that year he obtained an appointment at the research laboratories of British Schering Ltd. at Alderley Edge. He was elected an Associate of the Royal Institute of Chemistry in 1943. In 1947 he obtained the degree of Ph.D. for work carried out at Alderley Edge, and at about the same time he moved to the research laboratories of Albright and Wilson, where he remained until his death under tragic circumstances in the early hours of the morning of June 4th, 1955.

Philip Carter was a most conscientious worker and a first-class experimentalist. His bench and his laboratory records were a model of neatness and efficiency. His main interests were in organic chemistry and analytical methods. He was the author of three publications in the *Journal* (1948, 143, 147, and 150) on " Acyl Derivatives of *p*-Aminobenzenesulphonylguanidine " (with D. H. Hey and D. S. Morris), " The Action of Chlorine on Aqueous Solutions of Ammonium Sulphinates " (with D. H. Hey), and " Synthetic Œstrogens of the Triphenylethylene Series " (with D. H. Hey). He was a member of the sub-committee on organophosphorus insecticides of the Ministry of Agriculture, Fisheries and Food and the Association of British Insecticide Manufacturers. His quiet and modest personality and his friendly disposition made him much liked and respected. He was a keen tennis player and excelled in dinghy racing. He took part in national and international races both on inland waters and at Falmouth and the Isle of Wight. Those who knew him will treasure the memories of his somewhat shy and boyish manner, of his sincerity and integrity, and of his good fellowship. His ambition was to apply his scientific training towards any ends which would improve the well-being of mankind, and this high ideal was faithfully reflected in his character. He leaves a widow and two young sons to whom our deepest sympathy is extended.

D. H. Hey.

SALAH ELDIN SAID EL WAKKAD.

1918—1955.

The death of Salah Eldin Said El Wakkad on September 21st, 1955, in the London Clinic, London, cut short a career of great promise, and came as a great shock to his colleagues and students in Egypt. He was born on August 18th, 1918, at Abbassieh, Cairo, and received his early education in the schools of the same district. He proceeded thence in 1935 to the University of Cairo, obtained his B.Sc. with First Class honours in Chemistry in 1939, and was appointed in the same year a demonstrator in the Chemistry Department, Faculty of Science. In spite of the severe conditions which prevailed at that time owing to the outbreak of the second World War, El Wakkad, full of determination and enthusiasm, started research in the field of electrochemistry under the direction of Professor A. R. Tourky. He investigated with success the relation between solubility and particle-size, as observed with silver oxide of very high purity, and was awarded the M.Sc. degree in 1942. He started then investigating oxide-film formation on metals and the evaluation of the standard electrode potentials. In 1944 he was awarded the Ph.D. degree and offered a lectureship in the Department. The important achievements in these investigations appeared in a series of papers in the *Journal of the Chemical Society*, and the *Journal of Physical and Colloid Chemistry*, during 1948—1949.

Shortly after obtaining his Ph.D. degree El Wakkad started to suffer from mal-functioning of his liver. He showed some improvement now and then, but he became a chronic sufferer of this malady, his health remaining, from then, always very delicate. Nevertheless, he ably encouraged and supervised his younger research workers, and extended his investigations to

mercury, lead, tungsten, and antimony electrodes. A group of papers on these studies carrying his name appeared in various scientific journals.

Early in the Autumn of 1949 he went on a study leave to Liverpool, and joined there the school of electrochemistry under the direction of Dr. A. Hickling. He became acquainted with the oscillographic technique of studying anodic behaviour, and applied it to antimony and cobalt anodes.

At the end of 1950, after his return to Cairo, he was promoted Assistant Professor of Inorganic and Physical Chemistry. Then he became interested in the anodic behaviour of metals at very low current densities. He conducted a great number of investigations in this direction on nickel, copper, palladium, gold, tin, zinc, and some zinc–tin alloys. He published more than ten papers in this field.

In 1952, El Wakkad's research was rewarded by a Government Scholarship enabling him to continue his researches in some distinguished institutes abroad. In November, 1954, he left for the U.S.A. as an associate research assistant in the John Harrison Laboratory of Chemistry, University of Pennsylvania, where he joined Dr. J. O'M. Bockris, acting Professor of Physical Chemistry at that time. There, and perhaps for the first time, El Wakkad felt that more care should be given to his health. He consulted a number of specialists, but apparently without much progress, and early in the Summer of 1955 he returned to Egypt, completely exhausted and looking very unwell. Following his doctor's advice, and aided financially by the Egyptian Government, he left, two months later, for England for treatment, but unfortunately he died ten days after his arrival there. He was buried in his native birth-place, Cairo, on September 30th, 1955.

Outweighing El Wakkad's achievements as a research worker, his part in stimulating the creation and growth of the school of electrochemistry of Cairo University will ever remain as one of his conspicuous contributions. In addition to his scientific activities there seemed to be few general interests that failed at various times to receive his attention : scouting, camping, sport, social, and many other activities came within range of his active short life. His health which had been poor for many years failed to destroy his keen sense of humour which made him popular among his colleagues and earned him many firm friends. His great gifts as a lecturer were much appreciated by his many students, and his experimental and intellectual grasp of his line of research was a source of admiration to his colleagues and co-workers and will long be remembered.

He leaves a widow, herself a Cairo University graduate, and two daughters, and he will be always held in affectionate remembrance by all of us.

A. A. Moussa.

BERNARD JACQUES FLURSCHEIM.

1874—1955.

Bernard Jacques Flurscheim, who died on June 15th, 1955, in a hospital near his home in Fleet, Hampshire, was in his eighty-first year. So passes the last of the great pre-electronic builders of the theory of organic chemistry.

He was born on November 27th, 1874 at Baden-Baden. After a school education on classical lines at Baden and at Bournemouth, Flurscheim made his firsts cientific studies in the University of Geneva. Afterwards he worked with Werner at Zürich, and with Thiele at Strassburg. He took his Ph.D. in Heidelberg in 1901. In 1905 he set up his house in Fleet, in the garden of which he built the laboratory where he worked until other duties claimed him in the first World War. For the periods 1905—1907 and 1925—1928 he worked in the Royal Institution in London.

In his main scientific work, the provision of organic chemistry with a theoretical framework, Flurscheim was natural successor to both Werner and Thiele. He started from Werner's ideas of the divisibility of chemical affinity when discussing its distribution in molecules; and it ranks as a major and lasting discovery that his schemes of distribution involve a generalized idea of unsaturation and of Thiele's conjugation, as is today so readily appreciated in electronic terms.

Flurscheim's first two papers published in 1901—2 described experimental investigations of limited scope in the field of preparative organic chemistry. But in 1902 appeared also his

first paper of general chemical importance. In it he propounded the first serious theory (as distinct from a rule) of orientation in aromatic substitutions, evolving for this purpose an idea of the attributes of chemical affinity, which was of so general a nature as to form the outline of a theory of organic chemistry. He assumed that chemical affinity, even apart from unsaturation in the conventional sense, was continuously divisible, and was partly in the bonds and partly free. He supposed that an atom, such as bivalent oxygen, which has the intrinsic ability to increase its valency, would, when bound to an aromatic carbon atom, make a large affinity-demand on the latter, leaving it with little affinity for its other bonds, and little free affinity. This atom would thus make only a small affinity-demand on the next atoms; and thus the disturbance would be propagated, and an alternating distribution of bound, and free, affinity would be set up; which would give to *ortho*- and *para*-carbon atoms an excess of free affinity, and so lead to *ortho-para*-orientation. On the other hand, a substituent atom in its highest valency state, such as the nitrogen atom of a nitro-group, was regarded as an atom whose resources of affinity were already overtaxed; and therefore, it would be unable to make more than a small affinity-demand on a nuclear atom to which it was bound, and would thus set up the other possible alternating distribution of bound and free affinity in the benzene ring, leading to *meta*-orientation.

Flurscheim's theory played an important rôle in the development of the modern theory. For it embodied a widened idea of unsaturation and of conjugation, recognising in the power of an atom to increase its covalency (or to share its unshared electrons, as we should now say) a condition which could, similarly to a double or triple bond, disturb the distribution of affinity in its neighbourhood. It described the affinity redistribution resulting from this kind of unsaturation quite correctly in its formula covering *ortho*- and *para*-orientation, a formula which could be, and indeed was, directly translated into electronic terms. Flurscheim's theory, even in this early stage of its development, thus provided much of the pattern of what is called the electromeric effect in the modern theory of organic chemical reactivity.

In 1905 he entered on another field of application of his ideas, and one which again implied a principle of general importance. A few years earlier Gomberg had discovered what he called triphenylmethyl, which was a colourless solid, giving a yellow reactive solution in which the molecular weight of the solute was approximately twice what would have fitted Gomberg's view of its nature. Flurscheim suggested that the solid was hexaphenylethane, and that in solution it underwent a small equilibrium degree of dissociation to yellow reactive triphenylmethyl. (Three years later Schmidlin experimentally confirmed this interpretation.) Flurscheim further explained that the reason why triphenylmethyl had sufficient stability to coexist with hexaphenylethane in solution was that the phenyl groups had such an affinity demand that the three between them could use up the affinity of the methyl carbon atom, except for a considerable residue of free affinity. This was Flurscheim's first application of his affinity redistribution theory to a problem of equilibrium, as distinct from one of kinetic reactivity. In thus extending his domain from kinetics to thermodynamics, he showed that his valency redistributions apply, not only to activated states, but also to normal molecules. Today with the aid of the quantum theory, we re-express this too in electronic terms, and call the result mesomerism or resonance. In his example, he was giving a preliminary description of mesomerism in the triphenylmethyl radical. Thus, in combination with his previous work, the new contribution set the pattern of the mesomeric effect in the modern theory.

In two papers published in 1909—1910, Flurscheim made another thermodynamic application, *viz.*, to the strengths of acids and bases. These phenomena involve obvious polar effects, and also, as Flurscheim was the first to show, steric effects, so that their discussion needed the whole apparatus of a theory of organic chemistry. It is interesting to note the extent to which the integrated pattern of theory offered by Flurscheim corresponded to that of the modern theory, and also how much of the one theory could be directly translated into the other. Three superposed effects were recognised. One was the effect of the electropolar quality of affinity: here Flurscheim was only taking over ideas earlier established by Michael, Vorländer, and others: he was taking over, and was handing on, what has since become re-expressed in the inductive effect. Another effect was that of affinity quantity, as determined by the redistributions originating in different degrees of generalised unsaturation: this played the same part as does the mesomeric effect in the modern theory, and could, for example, be made responsible for the lower acid-strength of *p*-anisic than of benzoic acid, despite the electronegativity of the methoxyl group. The third effect was that of steric hindrance, which causes benzenoid *ortho*-groups, no matter whether they are electronegative or electropositive, to make aromatic acids stronger and aromatic bases weaker: this also the modern theory accepts, with the difference that it allows

for the secondary, as well as for the primary steric effect, which latter is all that Flurscheim envisaged.

Flurscheim's theory of organic chemistry was largely, but not wholly, correct in form; and a hint that something might be amiss was contained in a result that he discussed in his first major paper of 1902. Holleman had shown that phenylnitromethane is *meta*-orienting, whereas by this theory it should be *ortho*- and *para*-orienting. Flurscheim attacked this problem experimentally, and thought that he had found the answer. In fact he had only disclosed further complications, which were not fully cleared up until 1929—with the net result that the original difficulty remained. However, until the late 1920's, very few facts had appeared in the literature which could not be accommodated in Flurscheim's theory. That there were any such facts can be ascribed to two errors of form in the theory, *viz.*, (1) that it treats quantity of affinity as separable from polar quality, not recognising that a redistribution of affinity is necessarily one of polarity; and (2) that it does not allow for the great difference in the mobility of valency, as between saturated and unsaturated atoms. The first of these certainly, and the second possibly, are errors that could not have been corrected, excepting in the way in which they were, *viz.*, in the course of a translation of the theory into electronic terms. Therefore, we may say that Flurscheim's theory was about as correct as it was possible for a pre-electronic theory to be: indeed, its largely correct form made the task of remoulding it in electronic terms a particularly easy one for others.

Flurscheim never participated in this remoulding, for the basic reason that he did not accept the shared-electron theory of the chemical bond. His objection was that this theory of the bond purported to be physical, and hence must be electrostatic, since physics provided no other strong forces; and plenty of reason could be given why the bond forces could not be electrostatic. Therefore he concluded, the electrons " stay in the atoms," which are bound by some forces that physics did not recognise. Before Heitler and London's work of 1927, this argument was unanswerable. Flurscheim was good at unanswerable arguments, as came to be realised by some who opposed his theories. Moreover, Flurscheim's intellectual integrity was such that he was not prepared, as some were at that time, to make unphysical statements about a physical entity, the electron.

The experimental work which Flurscheim carried out, much of it single-handed in his laboratory at Fleet, was almost entirely directed to the control of his theoretical ideas. It was as an accidental result of this work that he made his outstanding discovery in the field of applied chemistry, that of tetranitroaniline (TNA), perhaps the most powerful contemporary explosive, which he described in 1910, and again much more fully in 1921. The accident was one he sometimes regretted, inasmuch as it led him into commercial work, to which he was not well suited. However, it enabled him to render notable service during the first World War, when, at the request of the late Lord Moulton, he undertook supervision of the large-scale manufacture of this explosive in the United States. During the second world war he worked as gas identification officer for the A.R.P. authorities. Other by-products of his experimental investigations on aromatic substitution include the discovery of pentanitroaniline and of hexa-aminobenzene. His last paper, in 1932, was on the addition of alcohols to nitroethylenes, a subject on which he had published an investigation 30 years earlier.

Flurscheim did not make human contacts easily or treat them lightly. He was devoted to his family, and to a few firm friends. In 1902 he married Norah Kathleen Northover, only daughter of the late Henry Northover of Fonthill, Wiltshire. He is survived by her, as by their son and daughter. His chief recreations were travel and climbing. In 1903 he visited New Zealand, where his father, Michael Flurscheim, lived, and there he made acquaintance with the New Zealand Alps. He knew the Alps of Europe intimately. His intellectual life was just as vigorously lived; for he had strong literary gifts and interests, as well as the penetrating analytical mind of the scientist. His early classical education started in him a long career of erudite classical scholarship. But this was only his second passion. His first was a deep devotion to pure science, for which he laboured, often alone, without any thought of material reward, or any motive towards a personal career. His greatest wish was to serve science, and in particular to elevate the status of organic chemistry by providing it with rational scientific system. Certainly the major and essential part which he played in the development of such a system for organic chemistry will immortalise his name as long as chemistry is studied.

C. K. Ingold.

HAROLD AUGUSTINE TEMPANY.

1881—1955.

HAROLD AUGUSTINE TEMPANY, the well-known expert on tropical agriculture, was born at Richmond, Surrey, on July 23rd, 1881. His father, Thomas William Tempany, was a solicitor practising in Bedford Row, a specialist on the rights and position of women after marriage, and widely interested in the local affairs of Richmond; among other activities he founded the Richmond Athenæum, a literary society before which he frequently lectured. His mother, Emily Ann, daughter of Job Palmer, was a descendant of the Tigou family who came to this country with William III, one of whom designed the Tigou screen in Hampton Court.

He therefore grew up in an atmosphere of literary activity and artistic tradition. His own taste, however, was for scientific work and after passing through the County School at Richmond he proceeded to University College, London, his father's old College, but instead of Arts or Law he studied Chemistry under Sir William Ramsay. After graduation he did not elect to follow an academic career or to accept one of the industrial appointments then opening up; the spirit of adventure was abroad and in 1903 he applied for and obtained the post of Assistant Agricultural Chemist in the Leeward Islands, attracted by the nature of the work and a desire to see what the West Indies were like.

It was a new and somewhat uncertain profession, but he was always a pioneer. The West Indies were still suffering severely from the competition of European sugar made from sugar beet and subsidised by the various Governments, but the Agricultural Department founded by Joseph Chamberlain and put under the direction of Francis Watts, a Kew man, was already improving the position by introducing new crops and better canes and by controlling crop pests and diseases. Tempany had no agricultural knowledge but he had enthusiasm and a lively interest in the problems: from his centre in Antigua he applied his chemistry to such good effect that after six years, in 1909, he was appointed Government Agricultural Chemist and Superintendent of Agriculture and held this post for a period of eight years. His chemical work was concerned with local problems; his papers on the determination of sucrose were not only of great importance to the sugar cane industry but also of more general interest: they were on the effect of temperature changes in the polarimetric determination of sucrose, and on the effect of clarification with basic lead acetate on the optical activity and copper reducing power of sugar solutions.[1]

Thanks to the work of the various Departments the economic position improved and by 1911 the West Indies had become solvent.

Tempany did so well that in 1917 he was appointed Director of Agriculture in Mauritius. By this time he had a wide knowledge of sugar cane, the chief crop of the island, and was able to organise experiments on its irrigation and manuring, the results of which if generally adopted would considerably improve their yields. Most of the planters, however, are French, retaining their old language and culture in spite of the island's having been in British possession since the Napoleonic wars: indeed Tempany related that some of the ladies made a point of not learning English. Fortunately Tempany had a good command of the French language and this, combined with an attractive personality, a fine baritone voice, a sound taste in music, and a love of amateur theatricals, broke down the barriers and helped greatly to establish friendly relations with the planting community; he quickly gained their confidence, and his sound advice based on his previous knowledge and on his experimental results was well received. He was largely responsible for the establishment of the Sugar Cane Research Station, which was later converted into the Mauritius Sugar Industry Research Institute.

In 1924 he added to his other duties the Principalship of the newly established Mauritius College of Agriculture; he held this post till 1929 when he was appointed Director of Agriculture in the Straits Settlements and Federated Malay States. This in effect was a new post: for some years before that date the Department of Agriculture had been in the charge of a Civil Servant as Secretary under whom rubber research had been transferred to the recently founded Rubber Research Institute, thus depriving the Department of one of its main functions, but of course releasing its energies for other work. Rubber was then by far the most important crop in the country. But the rubber market was very depressed, output was being restricted,

[1] West Indian Bull., Vols. VI, VII; *J. Soc. Chem. Ind.*, 1908, **27**, 53, 191.

and the country was suffering economically. Like some of the other experts Tempany saw the unwisdom of relying too much on one crop and recognised that the agriculture of the country must be put on a broader basis and must include more cash crops as well as food crops so as to reduce the need for imports. This meant a radical reorganisation of the Department. All research was co-ordinated under a Chief Research Officer and all field work under a Chief Field Officer; both were of equal status and directly responsible to the Director: the old water-tight compartments thus broke down. Steps were taken to enlist the co-operation of the small cultivators as well as the planters and the Rubber Research Institute, and to secure the interest and sympathy of the rural community generally. Malaya's climate is not conducive to hard work, but Tempany's boundless energy overcame all difficulties and enabled him to travel widely so as to discover the possibilities of the different regions, while his infective enthusiasm and friendly interest in his staff secured their loyal support and an affectionate regard which he retained long after he had left the country.

Pineapples were already grown in Johore; he saw the possibility of developing a canning industry and promoted the necessary research and legislation; experiments were also made with cocoa, manila hemp, palm, coconut, and other oil-bearing plants. Rice was—and is—the chief food: work on its improvement by breeding and selection already begun by Jack and Jagoe was further developed. Two large blocks of laboratories were started at Headquarters in Kuala Lumpur for the necessary chemical and biological investigations. At the same time there was a parallel development of the Extension Service to put the results into practice. A School of Agriculture was established on the main Experimental Station at Serdang: this later developed into the College of Agriculture. A stream of publications was issued in English, Malay, Chinese, and Tamil to ensure as wide a dissemination of sound information as possible. Agricultural shows were organised for the further education of the cultivators and the public.

In addition to his official activities he took an active interest in the Malaya Section of the Royal Institute of Chemistry.

His successes in Mauritius and Malaya marked him out for further advancement and in 1936 he was transferred to the Colonial Office in London to assist the Agricultural Adviser, Sir Frank Stockdale, in the vastly increased work being undertaken for agricultural developments in the Colonial Empire. Here he did so well that in 1940 he was appointed to succeed Sir Frank when the latter became Comptroller of Development and Welfare in the West Indies. This post involved considerable work on Committees and Commissions. He was always keenly interested in the expansion of the research institutions. He was largely instrumental in the establishment of the West African Cocoa Research Institute, the need for which he realised directly the swollen-shoot disease appeared and before its devastating effects became widespread; and also in the establishment of the East African Agriculture and Forestry Research Organisation which now has well appointed laboratories at Maguga near Nairobi under the direction first of Sir Bernard Keen and now of Dr. E. Walter Russell. He served on the Governing bodies of the Imperial Institute, the Imperial College of Tropical Agriculture, the Empire Cotton Growing Association, and on the London Advisory Committees for Rubber Research in Ceylon and Malaya and for the West Indian Sea Island Cotton Association of which he was for a long period the Chairman; he was also a most helpful member of the Editorial Committee of the *Empire Journal of Experimental Agriculture*. Throughout he retained his interest in chemistry: during the period 1940—1943 he was a member of the Chemical Council and a Vice-President of the Royal Institute of Chemistry.

In 1946 he retired from the Colonial Office on age limit, and his distinguished services were rewarded by a Knighthood; he had already in 1933 been awarded the C.B.E. and in 1941 the C.M.G. He was however far too energetic to give up work. Besides continuing to serve on various Committees he became editor of Messrs. Longman's series of books on tropical agriculture and in 1949 of *World Crops*, a new journal started by Leonard Hill, Ltd. He had already written in 1930 a book on "Principles of Tropical Agriculture" with G. E. Mann, and was the principal author of the Colonial office handbook on West Indian agriculture; he also wrote a detailed account of Soil Conservation in the British Colonial Empire, based on replies to questionaires sent out by the Commonwealth Bureau of Soil Science and published by that body in 1949. This question of soil conservation had always interested him as far back as his Mauritius days.

In his numerous and widespread activities he was greatly helped by his gift of making and keeping friends. His colleagues all liked him and were always ready to support him in any way they could; he retained for them a great affection and his personal mail was heavy but very gratifying to him. He married in 1911 Annie Frances Agnes, eldest daughter of

Robert Goodwin, and they had one son born in 1920 in Mauritius. She died in 1945. In the following year he married Kate, youngest daughter of William Welfare, who survives him.

He was still in good health when news came of the death of his only son in Kenya. The shock brought on a stroke from which he never recovered; he lasted only a few hours and died at his home in Kensington on July 2nd, 1955. Many of those interested in tropical agriculture felt that they had lost a good friend.

The author acknowledges with thanks his indebtedness to several of Tempany's friends and colleagues, especially D. H. Grist, J. N. Milsum, R. G. H. Wilshaw, and F. L. Okell, and to the Commonwealth Bureau of Soil Science for useful information on his life and work.

E. JOHN RUSSELL.

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